Vol. 33 No. 171 October, 1958

ARCHIVES OF DISEASE IN CHILDHOOD

CONTENTS

LONDON
BRITISH MEDICAL ASSOCIATION
TAVISTOCK SQUARE, W.C.1

YEARLY SUBSCRIPTION (6 NUMBERS) £4 4s. 0d. U.S.A. $13.50 SINGLE NUMBER 17s. 6d.

NOTICE TO CONTRIBUTORS

Papers for publication should be sent to the Editors, B.M.A. House, Tavistock Square, London, W.C.1.

Submission of a paper for publication will be held to imply that it contains original work which has not been previously published. Permission to republish must be obtained from the Editors.

Papers should be as concise as possible and illustrations kept to the minimum. Manuscripts should be typewritten top copies in double spacing. They should have been carefully revised, and alterations in proof, apart from printers' errors, are not permissible.

Photographs and photomicrographs should be submitted unmounted. Drawings and diagrams should be boldly drawn in black ink on stout white paper. Any necessary lettering may be lightly inserted in pencil.

Overseas contributors should nominate somebody resident in Great Britain willing to correct their proofs and deal with the subject of reprints.

Current numbers of the *Archives of Disease in Childhood* should be consulted for information concerning standard abbreviations, etc. In references to papers in the text the year of publication in parenthesis should follow the author's name. References at the end of the text should be in alphabetical order of authors' names, and titles of journals should be abbreviated according to the *World List of Scientific Periodicals*. Book titles should be followed by the place of publication.

Failure to observe the above directions may result in the return of typescripts to authors for correction, with consequent delay in publication.

Twenty-five reprints are supplied free. Further reprints must be ordered when returning proofs.

Subscription. £4 4s. 0d. per annum, post free.

Applications for advertising space should be made to the Advertisement Manager, British Medical Association, B.M.A. House, Tavistock Square, London, W.C.1.

SEVERE INFANTILE HYPERCALCAEMIA WITH SPECIAL REFERENCE TO THE FACIES

BY

M. C. JOSEPH and D. PARROTT

From the Department of Child Health, Guy's Hospital

(RECEIVED FOR PUBLICATION APRIL 30, 1958)

In 1932 Lightwood described a child aged 2 years whose illness resembled the terminal stages of severe infantile hypercalcaemia. Later Butler (1951) and Fanconi (1951) each reported similar cases and they then discussed their findings in a joint paper (Fanconi, Girardet, Schlesinger, Butler and Black, 1952). Since then there have been several reports of the severe form of this disease in this country (Creery, 1953; Dawson, Craig and Perera, 1954; Lowe, Henderson, Park and McGreal, 1954; Russell and Young, 1954; Schlesinger, Butler and Black, 1956). The incidence in America is less but recently a few cases have been reported (Sissman and Klein, 1956; Daeschner and Daeschner, 1957; Bongiovanni, Eberlein and Jones, 1957).

Lightwood and Stapleton (1953) believed that the severe type of infantile hypercalcaemia was a different syndrome from the mild type and they suggested that each should be labelled descriptively until more was known about them. They pointed out that in the mild form (Lightwood, 1952; Payne, 1952), the prognosis was good, but that in the severe form renal damage and mental retardation commonly occurred. This division into mild and severe forms is probably artificial because gradations between the two forms have emerged. We here describe three infants who were severely affected, and, in support of the conception of intermediate forms, a fourth infant who was moderately severely affected; in addition, this infant showed some of the features of infantile renal acidosis (Lightwood, 1935). We also report our observations on the facies as it is often a prominent and diagnostic feature of the disease.

Case Histories

Case 1. B.G. was the second child of healthy parents. Pregnancy and delivery were normal, and her birth weight was 7 lb. 12 oz. She was breast fed for the first three weeks, and then as lactation failed she was fed on National Dried Milk, half cream for six weeks and subsequently full cream. About 400 units of vitamin D (National Cod Liver Oil compound) were given daily.

Vomiting dated from birth, and usually occurred about half an hour after a feed; it was often bile stained. Initially she took her feeds fairly well but as her gain in weight was unsatisfactory she was admitted to a hospital at the age of 3 months; while there regurgitation occurred and a barium meal was normal; she was discharged home after four days. Her vomiting and failure to thrive continued, and at the age of 4 months one of us first saw her at an infant welfare clinic. Her weight was then 9 lb. 14 oz., and physical examination showed an apathetic infant, with a wide mouth, epicanthic folds and a concomitant squint (Fig. 1); a loud blowing systolic

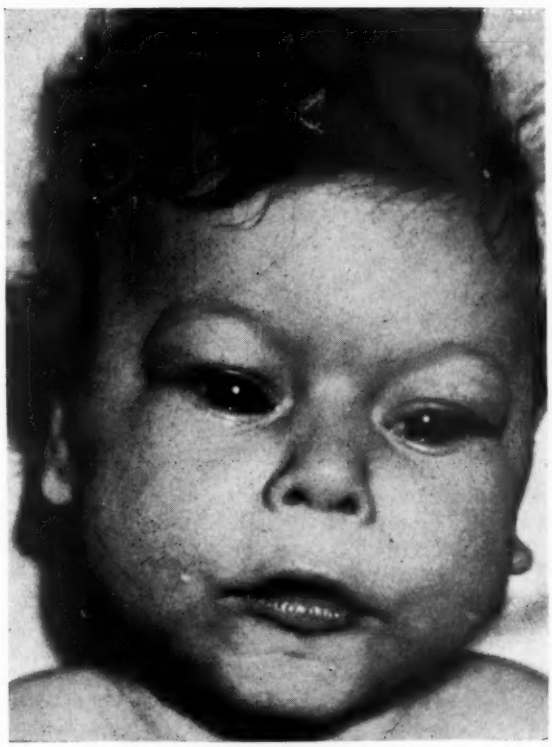


FIG. 1.—The facial appearance.

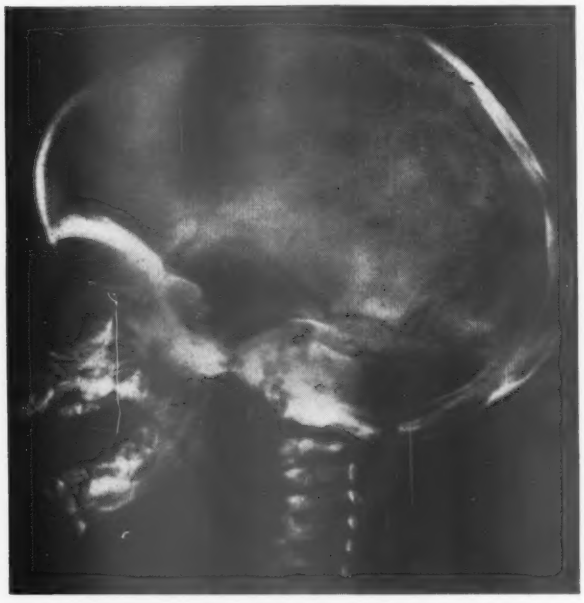


FIG. 2.—Case 1. Increased density at the base of the skull.

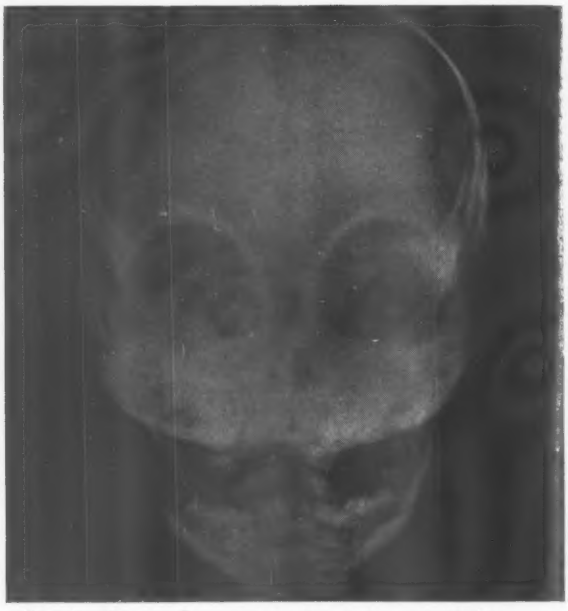


FIG. 3.—Case 1. Increased density of the periorbital bones.

murmur internal to the apex was present and the systolic blood pressure was 130 mm. Hg. A provisional diagnosis of severe infantile hypercalcaemia was made and she was admitted to Guy's Hospital for further investigation.

INVESTIGATIONS. The results of investigations on admission are shown in Table 1. The main abnormality was the raised blood urea. The serum calcium was regarded as a high normal. The serum cholesterol was normal. The electrolytes were normal. Radiographs of the skeleton showed increased density at the base of the skull (Fig. 2), of the periorbital bones (Fig. 3), at the ends of the long bones and the upper and lower borders of the vertebrae.

Serial biochemical estimations were made over the first five weeks (Table 2). Four weeks after admission the serum calcium level was unequivocally raised to 13·3 mg. %. The serum cholesterol was normal on three occasions (132 mg. %, 125 mg. %, and 117 mg. %).

TABLE 1
EARLY INVESTIGATIONS

		Blood Count		Urine				Blood Chemistry									Radiographs showing increased Density					
Case No.	Age (months)	Haemoglobin (g %)	White count (thousands/c.mm.)	pH	Albumen	White cells in deposit	Culture	Calcium (mg. %)	Phosphorus (mg. %)	Phosphatase (units K.A.)	Urea (mg. %)	Cholesterol (mg. %)	Sodium (mEq/l)	Potassium (mEq/l)	Chloride (mEq/l)	Bicarbonate (mEq/l)	Base of Skull	Periorbital Bones	Ends of Long Bones	Borders of Vertebrae	Pelvis	Ribs
1	4 5	11·2	10	acid	nil	±	—	11·4 13·3	4·2 9·6	13 16	57 100	132 117	137	4·4	101 101	19·8 20·4	yes	yes	yes	yes	no	no
2	5	9·5	27	4	+	+	—	13	3	6	97	160	152	3·7	102	24	yes	yes	yes	no	no	no
3	24 60			8 acid	nil nil	— —	— —	12·4 9·5	6·2	21	133 73	320 302			97	22·5	yes no	yes no	yes	yes no	no no	no no
4	5½	10·8	12	6	nil	+++	*Esch. coli*	10·9 11·5			35			4·6	109	16						no
	7 12			neutral	+	++	*Proteus*	11·2 14 9			60	315			113	18·8				yes	yes	no
								15·8 14·6			130	200	146	4·6	113	18·8	yes	yes	yes	yes	yes	no

FIG. 4.—Case 1. Post mortem radiograph of kidney showing deposits in the pyramids.

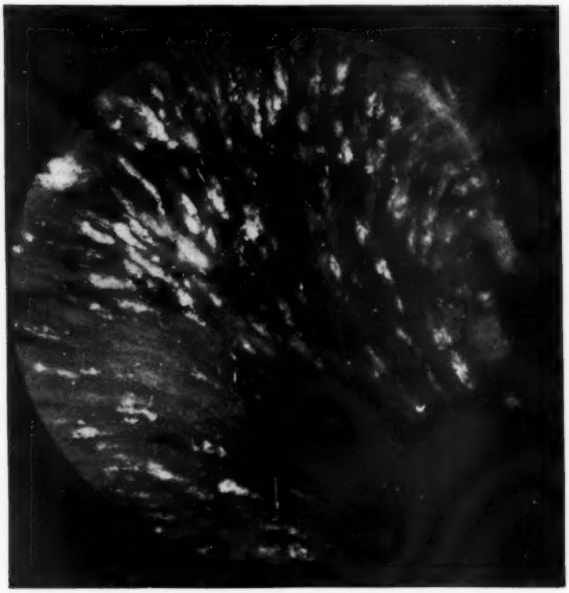


FIG. 5.—Case 1. Macrophotograph of kidney showing deposits in the pyramids (× 10).

TREATMENT AND PROGRESS. Treatment with cortisone by injection was started when she was just over 21 weeks old (Table 2); the dose varied but initially was 75 mg. daily for four days, and then 50 mg. daily. She was fed on National Dried Milk, but no added vitamin D was given. The serum calcium level dropped to 10·4 mg. % five days after starting cortisone, and apart from one raised value of 12·0 mg. % 10 days afterwards, it remained normal (Table 2). While she was on cortisone therapy a calcium balance was attempted but this was abandoned after 42 hours because she developed a severe rectal prolapse. She made slow progress, being difficult to feed, vomiting and failing to gain an adequate weight. A milk mixture which resulted in an intake of not more than 100 mg. of calcium daily was given but her anorexia became worse. At the age of 28 weeks she developed diarrhoea and the cortisone was stopped. The diarrhoea subsided, but her vomiting persisted and the serum calcium levels rose, the highest being 19 mg. % at the age of 9 months. The blood urea varied between 57 and 100 mg. %. Radiographs of the skull and the ends of the long bones showed an increase in density.

TABLE 2

CASE 1. BLOOD CHEMISTRY BEFORE AND DURING TREATMENT WITH CORTISONE

Age (Weeks)	Calcium	Phosphate	Phosphatase	Urea
16*	11·4	4·2	13	57
17	10·3	—	—	66
18	9·8	—	9	83
20	13·3	9·6	16	100
21	11·9	—	—	27
		Cortisone		
22	10·4	5·7	1	—
23	12·0	3·8	16	75
24½	8·8	—	—	—
25½	11·3	4·5	9	84
26	11·2	5·4	8	47
27	9·2	4·2	9	—
28	10·6	3·8	5	50

* Age on admission.

Cortisone therapy, 50 mg. daily, was started again, and she was discharged from hospital. Her symptoms persisted, however, and both her azotaemia and hypercalcaemia remained unchanged. At the age of 23 months she developed severe whooping cough; her blood urea rose to 150 mg. % and she died two days later.

NECROPSY (Dr. E. H. Bailey). The essential findings were that the kidneys weighed 15 g. (normal 45 g.). Both organs were pale. Thin streaks of calcium-like material were seen in the pyramids of both kidneys (Figs. 4 and 5). The heart weighed 75 g. (normal 55 g.). The left ventricle showed a well marked concentric hypertrophy. The right auricle was dilated and the right ventricle showed a little concentric hypertrophy. The edges of the mitral and tricuspid valves were thickened but there was no macroscopic calcification. The brain itself was normal but the right lateral sinus was completely obstructed by an ante-mortem clot. In the skull the basisphenoid and the bone forming the upper wall of the orbits were thickened. Other organs were normal.

HISTOLOGY (Dr. S. J. de Navasquez). The heart, stomach, spleen, thyroid, suprarenal glands and bone from the base of the skull were all normal. The liver showed severe passive congestion, and the lungs purulent bronchopneumonia. The intima of the aortic valve showed non-specific fibrous thickening. The cortex of the kidneys showed glomerular atrophy and periglomerular fibrosis (Fig. 6). In the medulla there were focal areas of calcium-like material which extended into and disrupted the collecting tubules in the vicinity

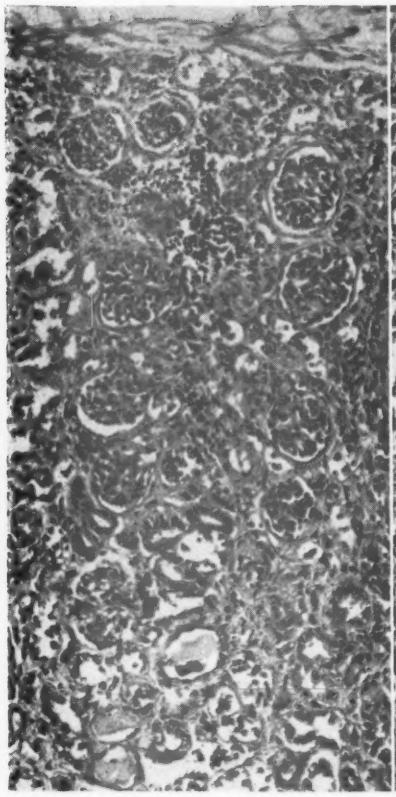


FIG. 6.—Case 1. Cortex showing glomerular atrophy and periglomerular fibrosis (H. and E. × 110).

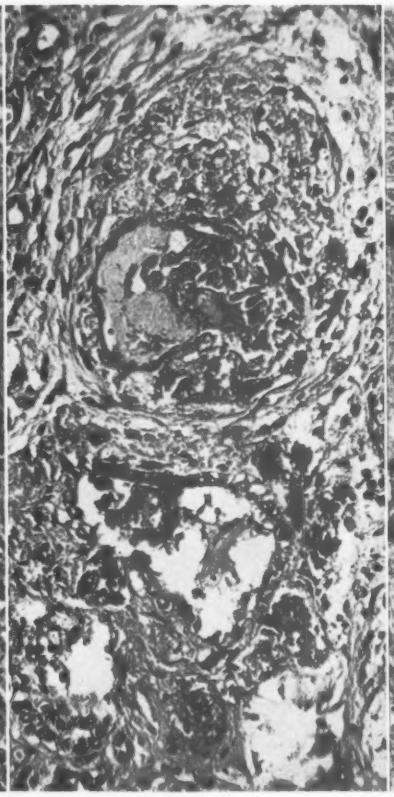


FIG. 7.—Collecting tubules showing intraluminal and subepithelial deposits of calcium-like material with disruption of the epithelium and interstitial fibrosis. (H. and E. × 175.)

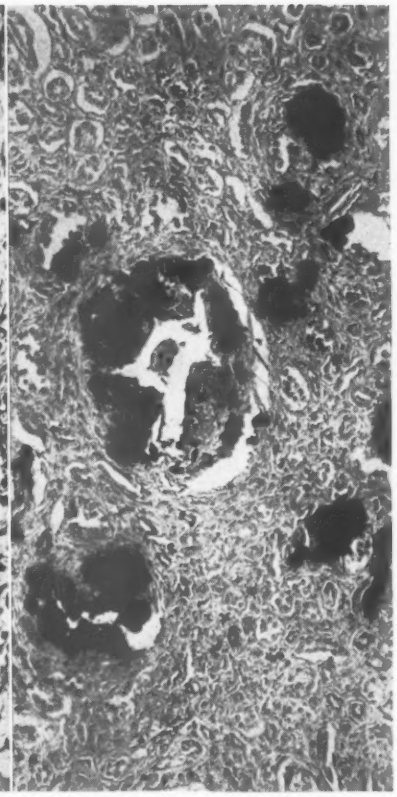


FIG. 8.—Medulla showing deposits of calcium-like material in the tubules. (von Kossa × 110.)

(Figs. 7 and 8). In addition, chronic focal pyelonephritis was present.

Case 2. B.D. was the second child of a family of three. Pregnancy was normal and her gestation period was 42 weeks; delivery was uncomplicated and her birth weight was 5 lb. 12 oz. She was breast fed for the first two weeks of life but when she was admitted to a hospital for severe conjunctivitis she was fed on half cream National milk. At this time she was noted to have an apical systolic murmur. She was in hospital two weeks and on discharge weighed 6 lb. 8 oz.

She progressed fairly well but vomited occasionally. At the age of 3 months her feeds were changed to full cream Cow and Gate milk. One month later she became listless and her vomiting became worse, and she was admitted to the Evelina Hospital. At this time she weighed 9 lb. 12 oz. Physical examination showed mild fever (100° F.), apathy, wasting, and loss of skin turgor. Her facies resembled that of Case 1, but in addition the inner third of her eyebrows was missing (Fig. 9). The pulse was regular at 130/minute and the heart was not enlarged. There was a loud systolic murmur maximal just internal to the apex. The blood pressure was 126/70 mm. Hg. There was marked hypotonia of the limb and trunk muscles. Other systems were normal.

INVESTIGATIONS. The results of investigations on admission are shown in Table 1. The urine contained albumen and an excess number of white cells; the serum calcium and blood urea were both raised. Radiographs showed increased density at the base of the skull, of the periorbital bones and at the ends of the long bones.

TREATMENT AND PROGRESS. Various feeds were tried, but her vomiting and anorexia persisted. She gained only 2 lb. in weight over a period of six months. A diet containing not more than 150 mg. of calcium daily was given for two months, but although her serum calcium levels became normal after six weeks, her symptoms persisted. Two weeks later, she was given normal milk feeds and this coincided with a gain in weight, which continued until her discharge four months later at the age of 19 months; at this time she weighed 16 lb. 14 oz., her hypotonia was less and she was able to sit up unaided. Her facies was unchanged. The serum calcium was 11·6 mg. % and the blood urea 40 mg. %.

She continued to progress very slowly, her weight at 2 years being 18 lb. 2 oz. Six months later she was readmitted weighing 19 lb. At this time she was beginning to say a few words and was walking with help; her squint was worse but the systolic murmur was now blowing and the systolic blood pressure was 110 mm. Hg.

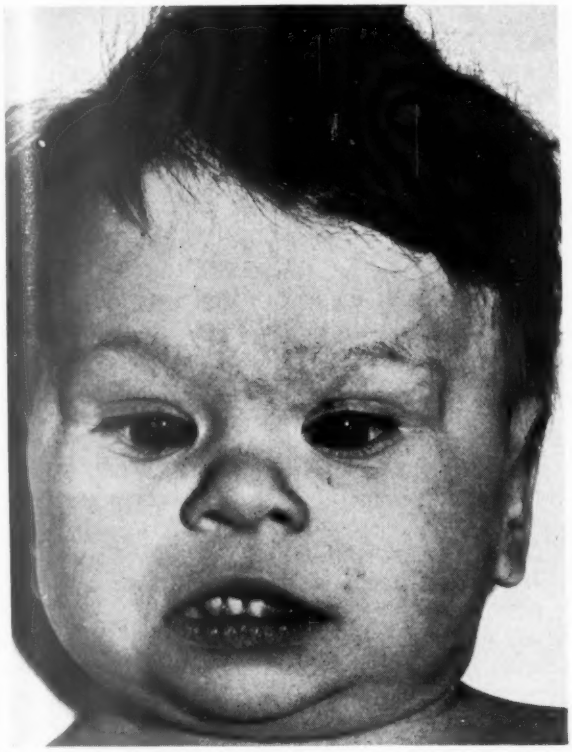


FIG. 9.—Case 2. The facial appearance; note loss of inner third of eyebrows.

The haemoglobin was 9 g. %, serum calcium 12·6 mg. %, phosphorus 4 mg. %, alkaline phosphatase 9 units (King Armstrong) and urea 65 mg. %. Radiographs of the skull and ends of the long bones showed a decrease in density.

A calcium balance was done when she was 2¾ years old and, following this, cortisone 15 mg. b.d. was given by injection. She became brighter, her appetite increased and she put on weight rapidly and consistently; the serum calcium fell to 7·8 mg. % but the blood urea remained elevated at 48 mg. % (Fig. 10).

Two months later the systolic murmur was less loud. The calcium balance was repeated while she was taking cortisone. She was discharged at the age of 3 years taking cortisone 25 mg. daily by mouth; this was continued for seven months. At the age of 4 years she weighed 24 lb. and was about 22 inches tall; her facies was unchanged but the systolic murmur was barely audible; the serum calcium was 9·8 mg. % and the blood urea 43 mg. %. Radiographs of her skeleton still showed some increase in density. Her I.Q. was 40.

Case 3. The clinical features of this patient have been already described (Schlesinger *et al.*, 1956). Briefly, vomiting and anorexia began when he was 11 months old. He was investigated but no firm diagnosis was made until the age of 2 years when he was seen by Dr. Philip Evans who observed the facies, physical and mental retardation and a loud systolic murmur. The

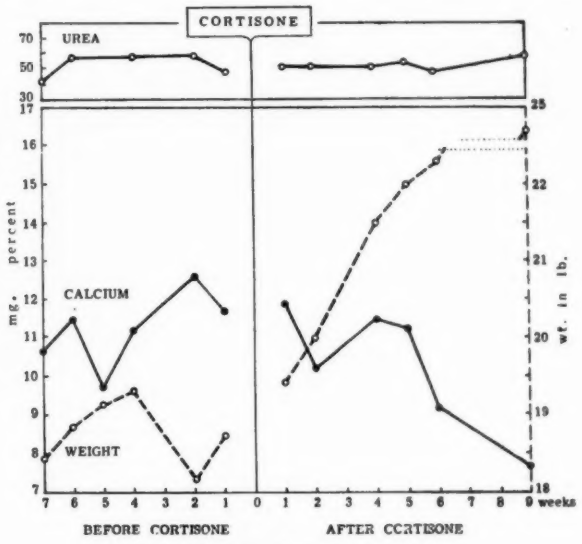


Fig. 10.—Case 2. Response to cortisone.

main investigations are shown in Table 1. The blood urea was 133 mg. %, serum calcium 12·4 mg. % and blood cholesterol 320 mg. %. The base of the skull and periorbital bones showed moderate increase in density.

Over the course of the next few months he began to improve slowly, the vomiting and anorexia became less and he began gaining weight. He was seen again at the age of 5 years, because of attacks of abdominal pain. He was a mentally retarded child whose behaviour resembled that of a 2-year-old; the facies and the squint were unchanged. No systolic murmur was present. Serum calcium, phosphorus and phosphatase were normal, but the blood urea was 73 mg. % and the blood cholesterol 302 mg. %; the urine, radiograph of the skull and intravenous pyelogram were normal and the bone age corresponded with the chronological age.

Case 4. P.B. was a second child; pregnancy and delivery were normal. His birth weight was 7 lb. 3 oz. As his mother had a history of tuberculosis he was never breast fed. For the first four months he was fed on half cream milk and subsequently on full cream milk. At the age of 4 months he began to vomit and the National Cod Liver Oil Compound (800 units of vitamin D), which he had been taking, was omitted. He continued to vomit and lose weight and at the age of 5½ months he was admitted to a hospital. Examination then showed a fairly fit-looking infant with a normal facies; his forehead was prominent, and his temples were narrow. No physical signs were present except those of mild dehydration. His weight was 14 lb.

INVESTIGATIONS. The results of investigations are shown in Table 1. The urine was infected with *Esch. coli*; the serum calcium and blood urea were normal, but the plasma chloride was raised and the bicarbonate lowered.

TREATMENT AND PROGRESS. Subsequent examination of the urine did not confirm the presence of an infection.

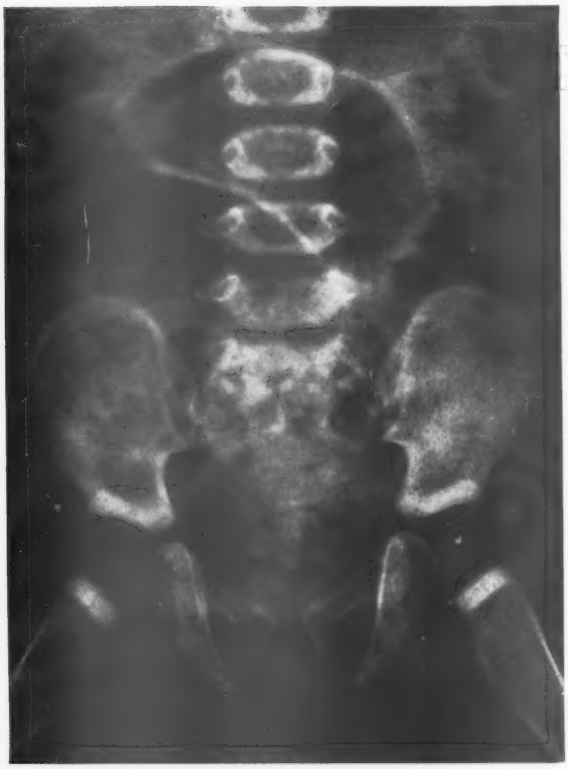


FIG. 11.—Case 4. Increased density adjacent to hip joints, of the iliac crests and of the superior and inferior borders of the lumbar vertebrae.

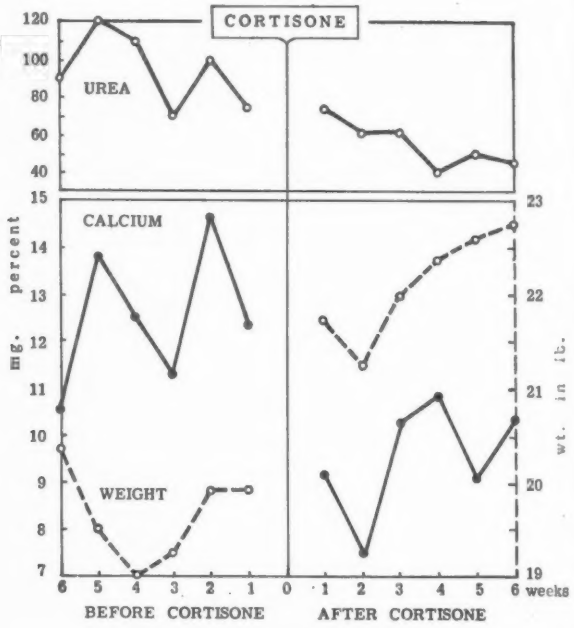


FIG. 12.—Case 4. Response to cortisone.

While in hospital he developed a series of upper respiratory infections. He vomited when he was fed on full cream milk, but when this was changed to half cream no vomiting occurred. He was discharged symptomless taking half cream milk. No firm diagnosis was made.

He progressed slowly until the age of 7 months when vomiting recurred and he developed severe constipation. He was admitted to Guy's Hospital. On examination there were no physical signs except those of constipation. The results of investigations are shown in Table 1.

In view of the previous and present findings, it was thought likely that he had infantile renal acidosis with hypercalcaemia and he was treated with a mixture of 10 gr. sodium citrate and 2·5 gr. of citric acid four times daily. He began gaining weight and the plasma bicarbonate rose to 26 mEq/l. and the plasma chloride fell to 104·6 mEq/l. When the alkali was discontinued the plasma bicarbonate fell to 16·2 mEq/l. and the chloride rose to 111 mEq/l. Treatment with alkali was reintroduced and he responded well, gaining 12 oz. in the first week.

Two months later he developed severe bronchitis and was readmitted. Examination at this time showed no physical signs additional to those of bronchitis; the systolic blood pressure was 110 mm. Hg; the blood urea was 130 mg. % and the serum calcium 9 mg. %. The α_2 and β globulins were increased. Radiographs of the skull, long bones, vertebrae and pelvis showed increased density (Fig. 11). Subsequent serum calcium levels remained high, rising to 15·8 mg. % and 14·6 mg. % on two occasions. He vomited periodically and gained weight slowly. A milk containing not more than 100 mg. of calcium daily was given for two months without appreciable effect clinically or biochemically. A calcium balance was performed at this stage, and following this he was given cortisone by injection, 25 mg. b.d. He responded well both clinically and biochemically; his serum calcium fell to 7·6 mg. % later rising to within normal limits (Fig. 12). He was discharged taking the same dose of cortisone by mouth. Three months later the calcium balance was repeated while he was taking cortisone.

His subsequent progress was good and he gained weight satisfactorily. The cortisone was stopped after 10 months. He continued to do well and at the age of 4¾ years he weighed 38 lb.; the blood pressure was 110/70 mm. Hg and no physical signs were present; there was no evidence of mental retardation. The urine was acid and normal. The blood urea was 44 mg. %, serum calcium 11 mg. % and phosphate 3·7 mg. %.

Radiologically the long bones were normal but the base of the skull and periorbital bones still showed some increase in density.

Calcium Balance Studies

Balance Methods. The patient was equilibrated on a constant calcium intake for three days and thereafter stools and urine were collected between stool carmine markers over a period of four days. The type of feed and calculated intake of vitamin D

are indicated in Table 3. A metabolic bed was used, and the stools were collected into cellophane-lined containers. In girls the urine was collected through a vulval mould and in boys through Paul's tubing. All receptacles for stools and urine were previously rinsed with distilled sterile water. Duplicate aliquots of stools, urine and a homogenate of a duplicate diet were digested with fuming nitric and perchloric acids. The digest was made up to volume and insoluble fatty acids were filtered off. After adjustment of pH, calcium was precipitated with excess oxalate and estimated by titration with standard potassium permanganate solution.

Table 3 shows the results of the balances. Cases 2 and 4 each had two balances, before and after cortisone therapy. Balances were attempted in Cases 1 and 2 in the early stages of their illness but were not completed as they were badly tolerated. Case 1 had a short balance lasting 42 hours while she was on cortisone, and although the results have been recorded, interpretation must be especially cautious. However, the figure of 38% retention is similar to that reported by Forfar, Balf, Maxwell and Tompsett (1956) and Morgan, Mitchell, Stowers and Thomson (1956) in affected infants of the same age while taking cortisone. The daily retention of calcium in Case 2 was 30% which is between one and a half and three times more than normal at this age (Daniels, 1941; Watson, McGuire, Meyer and Hathaway, 1945; McLean, Lewis, Jensen, Hathaway, Breiter and Holmes, 1946; Irving, 1950). The daily retention in Case 4 was about normal when expressed as a percentage of intake but in absolute figures (137 mg. and 248 mg.), both children retained between one and a half and three times normal (Shohl, 1939; Holmes, 1945; Mitchell, Hamilton, Steggerda and Bean, 1945). Schlesinger, Butler and Black (1952) and Forfar *et al.* (1956) in affected children of similar age reported daily retentions of 74 mg. and 126 mg. of calcium (7·7% and 16% of intake).

Effect of Cortisone. The effect of cortisone on calcium retention is shown in Table 3. In Case 2 calcium retention increased from 30% to 37% and in Case 4 from 20% to 33%. The total intake varied in our children, but Watson *et al.* (1945) found that similar variations of intake did not influence the percentage retentions in normal children. The effect of cortisone on calcium retention which we observed was similar to that found by Fletcher (1957) in a boy of 3 years in whom the faecal calcium decreased when he was given 15 mg. of cortisone daily. However, although others (Bonham Carter, Dent, Fowler and Harper, 1955; Forfar *et al.*, 1956; Morgan *et al.*, 1956) have found that cortisone increases the faecal calcium and therefore reduces calcium retention, their studies were on younger patients in whom cortisone therapy had been of shorter duration. Nevertheless, we cannot satisfactorily account for the difference in these findings, especially as cortisone was so effective in reducing the serum calcium levels (Figs. 10 and 12).

The Facies

The unusual facial appearance was recognized by Butler (1951) and Fanconi (1951), and it has been used to help distinguish the severe from the mild type. How soon after birth it develops is unknown. The mother of B.G. told us that she thought the face was 'queer looking' at birth, and it was sufficiently characteristic at 4 months of age for the clinical diagnosis to be made (Joseph, 1956).

The facies in this disease has received less attention than some of the other features, but since it usually indicates severity, it is both an important diagnostic and prognostic sign.

There have been too few examples observed for all the facial variations and combinations to be known, and for a great many generalizations to be made, and the following notes are no more than an attempt to focus attention on some of the changes. One of the difficulties we have encountered is our ignorance of the range of normal, if any face can be called normal. The facial appearance in this disease is due to the presence of a combination of features, but we do not know which particular

TABLE 3
CALCIUM BALANCES IN CASES 1, 2 AND 4

Case	Age (yr.)	Diet	Daily Vit. D Intake (units)	Calcium (mg. %)	Urea (mg.)	Daily Cortisone (mg.)	Calcium (mg. daily) Intake	Faeces	Urine	Retention	%
1 B.G.	½	Milk	700	11·2	84, 47	50	1,255	700	72	473	38
2 B.D.	3¼	Mixed	12	11·7	31		455	255	63	137	30
	3½	Mixed	44	9·2	47	50	1,066	512	119	373	37
4 F.B.	2	Milk, egg	66	11	93, 73		1,208	890	70	248	20
	2¼	Mixed	78	12·1 14·1	80, 60	50	702	342	123	237	33

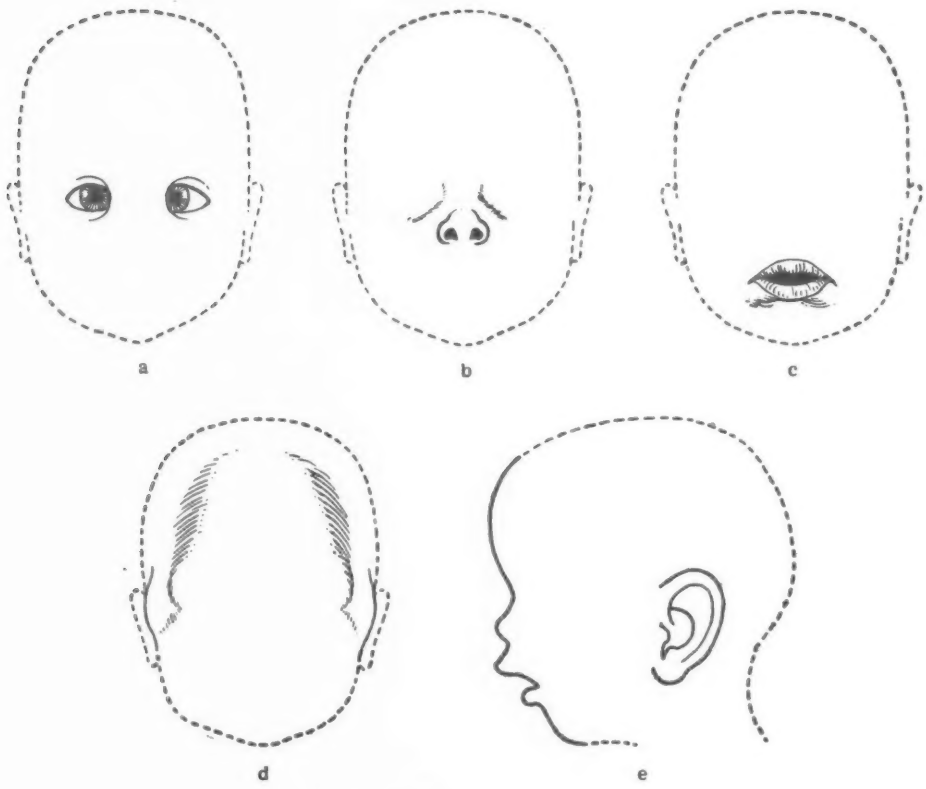


FIG. 13.—Components of the facies.

combination is necessary to produce the facies; indeed it is likely that different combinations will affect the facies, and this is probably what occurs.

Lowe *et al.* (1954) have described the facies as elfin-like; although we agree that this applies to the general shape of their face, it disregards their expression of misery and irritability. Surely elves have a sprightly air:

> 'Couronnés de thym et de marjolaine
> Les Elfes joyeux dansent sur la plaine.'
> *Leconte de Lisle*

The Individual Facial Features. Epicanthic folds and commonly a concomitant squint are present (Fig. 13a). The nose is pinched and retroussé, with the nostrils pointing forwards (Fig. 13b); because there is some filling in at the sides of and across the nose, the appearance has been likened to that of a pekinese dog (*British Medical Journal*, 1954). The upper lip is prominent and appears loose (Fig. 13e); it lacks the usual bow and the pars villosa may persist (Fig. 13c). The mouth is sometimes asymmetrical and is generally kept open, the lower lip hanging slackly. The temples are narrow (Fig. 13d). The profile is affected by the receding chin and by the rounded and sometimes prominent forehead (Fig. 13e). The ears may be large but are normally placed (Fig. 13e).

The ears have been described as being low set (Butler, 1951; Schlesinger *et al.*, 1952) but we think they appear so because these children frequently adopt a 'chin-up' position (Fig. 14). This deception is added to if the ramus of the mandible is short or if its angle with the body of the mandible is more acute than normal. The ear may also appear low if the vertex of the skull is deep; this was well illustrated when the father of an affected boy said he thought that his son's head was high rather than that his ears were low. Finally, a relative increase in the amount of the pinna below the meatus will make the ear appear low in the same way as a large ear may.

The profile of these infants runs downwards and backwards and therefore the Frankfurt line does not form even an approximate right angle with the profile. Although the ear appears low the external auditory meatus maintains a normal relationship with the base of the skull (Fig. 15).

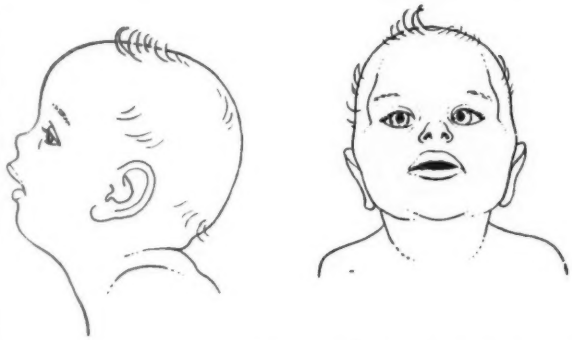


FIG. 14.—The ears appear low because the head is held extended

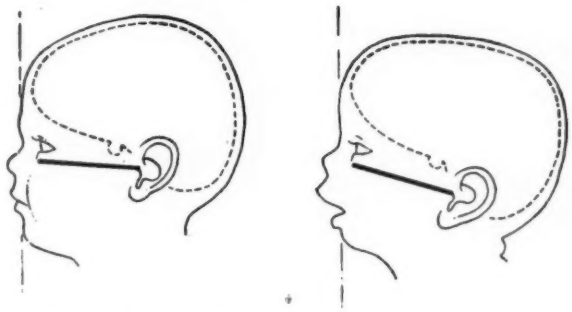


FIG. 15.—The Frankfurt line has been drawn and shows that the external auditory meatus has a normal relationship to the base of the skull.

The cause of the facies is unknown. Russell and Young (1954) have suggested that it is due to abnormal growth of the basisphenoid. Schlesinger *et al.* (1956) reviewed 10 cases of the severe type and all had both the characteristic facies and radiological changes in the skull. Our Cases 1, 2 and 3 were similar in these respects. Case 4 showed changes in the skull but except for a prominent forehead the facies was not characteristic. Of more than a score of infants with the less severe form of hypercalcaemia (Lightwood, 1952; Lowe *et al.*, 1954; Bonham Carter *et al.*, 1955; MacDonald and Stapleton, 1955; Forfar *et al.*, 1956; Morgan *et al.*, 1956; Rhaney and Mitchell, 1956; Kendall, 1957), none had radiological changes in the skull; in three the facial appearance was described as normal and in the remainder there was no comment. These observations suggest that the bone changes in the skull are responsible for the facies, but because some of the facial features seem to be due to alterations in the contours of the soft tissues, it is possible that the bone changes only play some part in the facial appearance.

Types of Idiopathic Hypercalcaemia

Stapleton and Lightwood (1953) suggested that certain clinical and radiological features served to distinguish cases of simple idiopathic hypercalcaemia with failure to thrive from those with general retardation and osteosclerosis. Lowe *et al.* (1954) have elaborated the differences. The former type is transient and relatively benign, without significant bone changes, systolic murmurs, hypertension or mental retardation. The latter type is sustained and severe, has bone changes, significant systolic murmurs, hypertension, characteristic facies, mental retardation and often a raised blood cholesterol. During the past few years, there have been many reports of infants with hypercalcaemia, and some have had features which have made it difficult to place them in one or other category. We are uncertain which criteria are valid in order to classify the affected infant. Transient and benign is no help as three infants who conformed to this type came to necropsy (Rhaney and Mitchell, 1956; Morgan *et al.*, 1956). Systolic murmurs may be present in both types; they were recorded in the simple type by Lowe *et al.* (1954), Creery and Neill (1954) and MacDonald and Stapleton (1955), but were absent in some of the severe cases collected by Schlesinger *et al.* (1956). Hypertension is also unreliable; MacDonald and Stapleton (1955) reported its presence in a simple case, while Creery (1953) and Lowe *et al.* (1954) found normal readings in two severe cases. Radiological changes in the bones are not absolute but increased density of the base of the skull has only been described in the severe forms, although it was not present in three patients who died (Rhaney and Mitchell, 1956). The characteristic facies has been described as only occurring in the severe form but Rhaney and Mitchell (1956) reported its absence in their three fatal cases. It is probably too early to evaluate the incidence of mental retardation, but in general the survivors in the simple group have developed normally whereas the few survivors of the severe form have been grossly retarded. The facies and bone changes in the skull usually occur together and indicate severity, with renal impairment and possible mental retardation. Cases 1, 2 and 3 had these changes and Case 1 died and Cases 2 and 3 are both grossly retarded (I.Q. 40). But absence of skull changes and of the facies does not necessarily indicate a good prognosis, as shown by the deaths reported by Rhaney and Mitchell (1956) and Morgan *et al.* (1956).

Creery (1953) has suggested that all grades of idiopathic hypercalcaemia occur and later others have supported this conception (Russell and Young, 1954; Lightwood, 1955). Case 4 was an example

of an intermediate grade. He resembled the simple type by the presence of a raised α_2 globulin, and the absence of abnormal facies, of hypertension, of a systolic murmur and of mental retardation. On the other hand, he resembled the severe type by the presence of bone changes in the skull, vertebrae and pelvis, by a raised serum cholesterol and by his slow recovery. Additionally he had some of the changes seen in renal acidosis. Lightwood (1952) and Payne (1952) reported that an associated renal acidosis was occasionally present in simple hypercalcaemia and Lightwood (1955) found this in six of 50 cases. In none of these patients, however, were there bone changes such as those found in Case 4.

As it is now recognized that the prognosis is not always good in the simple or so-called benign cases, it is suggested that the term 'benign' should no longer be used.

Necropsy Findings

The findings at necropsy and the histological changes have been described and discussed fully by Dawson *et al.* (1954), Lowe *et al.* (1954) and Schlesinger *et al.* (1956). Darmady and Stranack (1957, 1958) have microdissected a number of these kidneys and consider that the focal areas of deposit are probably a phosphate protein complex, and should at the moment be referred to as 'calcium-like'.

The changes in the kidneys found in Case 1 were similar to those previously reported. Although nephrocalcinosis was not diagnosed before death, calcium-like material was clearly seen in the cut surface of the kidney macroscopically and radiologically (Figs. 4 and 5). Darmady and Stranack (1958) have fully described their findings on microdissection of the kidney in Case 1 and we are grateful to them for allowing us to use their report and microphotograph. Briefly, they found focal areas of calcium-like material adherent to the basement membrane and projecting laterally from the proximal tubule wall. Similar areas were seen in the distal and collecting tubules (Fig. 16).

FIG. 16.—A portion of proximal tubule shows a plaque of calcium-like material adherent to the basement membrane and further areas are seen lower in the nephron. At the bottom left hand corner of the picture an albuminous case is seen lying in the lumen of the tubule. The architecture of the proximal tubule is normal. (× 280.)

Conclusion

The cause of infantile hypercalcaemia and an explanation of many of its clinical features remain unanswered. The exact incidence of the condition is unknown but Morgan *et al.* (1956) have pointed out that in Dundee between 1953 and 1955 it accounted for 4·6% of all medical admissions of children aged 6 to 12 months, ranking fourth in frequency after respiratory infections, feeding difficulties and otitis media. We do not know whether its incidence is diminishing, but if sensitivity to vitamin D (*Lancet*, 1954) is an important contributory factor, then the recent recommendation (Her Majesty's Stationery Office, 1957) that the vitamin D content of National Dried Milks and Cod Liver Oil Compound should be halved is likely to reduce the incidence of a disease which may cause physical and mental retardation, and sometimes death.

Summary

The clinical, radiological and biochemical features of four patients with severe infantile hypercalcaemia are described. In addition, one of the patients had renal acidosis.

Three patients were treated with cortisone, and in two the response was good; the third died and the results of necropsy are discussed. Balance studies on these three patients reveal an increased retention of calcium, and cortisone was found to augment this retention.

The individual features of the facies are illustrated

and discussed. It is suggested that patients having the characteristic facies are usually severely affected and are likely to have sequelae of mental retardation and renal insufficiency.

The types of infantile hypercalcaemia are discussed and it is suggested that the mild and severe types should not be considered separate syndromes.

Cases 1, 2 and 3 were under the care of Dr. P. R. Evans and Case 4 was under the care of Dr. R. C. Mac Keith. We thank Dr. W. H. H. Merivale for help with the calcium balances, and Dr. J. Dow for help with the interpretation of the radiographs. Miss S. Treadgold of the Medical Illustration Department contributed much to the section on the facies, and we thank her for her help and for the drawings. The remaining illustrations were made by the Photographic Department to whom we are indebted.

References

Bongiovanni, A. M., Eberlein, W. R. and Jones, I. T. (1957). *New Engl. J. Med.*, **257**, 951.
Bonham Carter, R. E., Dent, C. E., Fowler, D. I. and Harper, C. M. (1955). *Arch. Dis. Childh.*, **32**, 399.
British Medical Journal (1954). Leading article, **2**, 1155.
Butler, N. R. (1951). *Proc. roy. Soc. Med.*, **44**, 296.
Creery, R. D. G. (1953). *Lancet*, **2**, 17.
—— and Neill, D. W. (1954). *Ibid.*, **2**, 110.
Daeschner, G. L. and Daeschner, C. W. (1957). *Pediatrics*, **19**, 362.
Daniels, A. L. (1941). *Amer. J. Dis. Child.*, **62**, 279.
Darmady, E. M. and Stranack, F. (1957). *Brit. med. Bull.*, **13**, 21.
——, —— (1958). In the press.
Dawson, I. M. P., Craig, W. S. and Perera, F. J. C. (1954). *Arch. Dis. Childh.*, **29**, 475.
Fanconi, G. (1951). *Schweiz. med. Wschr.*, **81**, 908.
——, Girardet, P., Schlesinger, B. E., Butler, N. R. and Black, J. A. (1952). *Helv. paediat. Acta*, **7**, 314 and 335.
Fletcher, R. F. (1957). *Arch. Dis. Childh.*, **32**, 245.
Forfar, J. O., Balf, C. L., Maxwell, G. M. and Tompsett, S. L. (1956). *Lancet*, **1**, 981.
Her Majesty's Stationery Office (1957). Report of the Joint Sub-Committee on Welfare Foods.
Holmes, J. O. (1945). *Nutr. Abstr. Rev.*, **14**, 597.
Irving, J. T. (1950). *S. Afr. med. J.*, **24**, 601.
Joseph, M. C. (1956). *Brit. med. J.*, **1**, 1112.
Kendall, A. C. (1957). *Ibid.*, **2**, 682.
Lancet (1954). Leading article, **2**, 127.
Leconte de Lisle, C. M. R. (1925). *Oxford Book of French Verse*, p. 442. St. John Lucas.
Lightwood, R. (1932). *Arch. Dis. Childh.*, **7**, 193.
—— (1935). *Ibid.*, **10**, 205.
—— (1952). *Ibid.*, **27**, 302.
—— (1955). *Rev. port. Pediát.*, **18**, 335.
—— and Stapleton, T. (1953). *Lancet*, **2**, 255.
Lowe, K. G., Henderson, J. L., Park, W. W. and McGreal, D. A. (1954). *Lancet*, **2**, 101.
MacDonald, W. B. and Stapleton, T. (1955). *Acta Paediat. (Uppsala)*, **44**, 559.
McLean, D. S., Lewis, G. K., Jensen, E., Hathaway, M., Breiter, H. and Holmes, J. O. (1946). *J. Nutr.*, **31**, 127.
Morgan, H. G., Mitchell, R. G., Stowers, J. M. and Thomson, J. (1956). *Lancet*, **1**, 925.
Mitchell, H. H., Hamilton, T. S., Steggerda, F. R. and Bean, H. W. (1945). *J. biol. Chem.*, **158**, 625.
Payne, W. W. (1952). *Arch. Dis. Childh.*, **27**, 302.
Rhaney, K. and Mitchell, R. G. (1956). *Lancet*, **1**, 1028.
Russell, A. and Young, W. F. (1954). *Proc. roy. Soc. Med.*, **47**, 1036.
Schlesinger, B., Butler, N. and Black, J. (1952). *Helv. paediat. Acta*, **7**, 335.
——, ——, —— (1956). *Brit. med. J.*, **1**, 127.
Shohl, A. T. (1939). *Mineral Metabolism*, p. 50. New York.
Sissman, N. J. and Klein, R. (1956). *Clin. Res. Proc.*, **4**, 36.
Stapleton, T. and Lightwood, R. (1953). *Lancet*, **2**, 255.
Watson, E. K., McGuire, E. W., Meyer, F. L. and Hathaway, M. L (1945). *J. Nutr.*, **30**, 259.

CONGENITAL ABSENCE OF THE INTRAHEPATIC BILE DUCTS

BY

LEONARD HAAS and RICHARD H. DOBBS
From the Children's Department, The London Hospital

(RECEIVED FOR PUBLICATION MARCH 24, 1958)

Routine histological examination of the liver during the acute stages of neonatal obstructive jaundice, whether of biopsy or of autopsy specimens, reveals a variety of different pathological conditions.

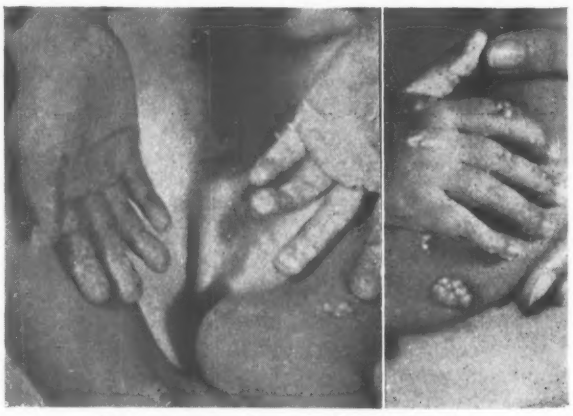
Congenital absence of the intrahepatic bile ducts appears to be a rare cause of obstructive jaundice in the newborn. The purpose of this paper is to draw attention to the condition by reporting two cases, and by discussing its main clinical and pathological features in the light of these two and eight other cases that have been found in the medical literature. One of the present cases was previously shown at a clinical meeting (Smythe and Dobbs, 1949) as a case of xanthomatosis, and later included in a monograph on this subject by Ahrens, Harris and MacMahon (1951) who considered the underlying pathology to be intrahepatic biliary atresia.

Neonatal obstructive jaundice with pale stools and dark urine has been common to all described cases, and in no way differed from that found in, for instance, congenital extrahepatic obstruction of the bile ducts or neonatal hepatitis. But, though the diagnosis was arrived at histologically in seven out of the 10 cases only after the age of 2 years, certain features common to the post-neonatal course of all of them appear to make the condition a recognizable clinical entity at least before the end of the first year of life.

Case Descriptions

Case 1. E.H., female, died aged 2 years 9 months. (Previously reported by Smythe and Dobbs, 1949; Ahrens *et al.*, 1951). She was the second child of healthy parents. The mother suffered from toxaemia in both pregnancies. The first child is alive and well. The birth was normal, the infant weighed 6½ lb. and was apparently healthy. Jaundice was noted on the second day of life and rapidly deepened. The serum bilirubin was not estimated at this stage. The stools became clay coloured and remained so for the first two months, after which they became yellow and sometimes brown. The urine is alleged not to have contained bile pigments during the neonatal phase of the disease though from the age of 5 months onwards tests for bilirubin were always positive. Pruritus was a troublesome symptom from the first few days of life: persistent scratching often led to excoriations and bleeding, and the child was always unhappy and fretful. Nevertheless feeds were taken well and she gained weight slowly. At the age of 20 months widespread deposits of yellow material appeared in the skin. At the same time pruritus became more marked and scratching was mainly aimed at these deposits which frequently bled freely.

The child's condition remained stationary and in September, 1948, at 2½ years of age, she was admitted to The London Hospital for investigation. She was then found to be a thin, undersized and unhappy child, 21 lb. in weight and 32 inches in height. There was moderate generalized jaundice of the skin and the conjunctivae. The body was covered with innumerable yellow, raised xanthomatous deposits, especially marked over the hands, elbows, ankles and legs (Figs. 1 and 2). Miliary xanthomata were found on the palms and soles and longitudinal yellow streaks in the creases of the skin and along the gum margins. Both liver and spleen were enlarged and palpable 1 inch below the costal margin, the liver edge



FIGS. 1 AND 2.—Case 1. Skin xanthomata.

being firm and smooth. A systolic murmur was audible over the praecordium.

The relevant investigations at this time were as follows: liver function tests: serum bilirubin, 4·5 mg. per 100 ml.; alkaline phosphatase, 36 units; serum proteins, 6·3 g. per 100 ml. (albumin, 4·1; globulin, 2·2); thymol turbidity, 2·5 units; cephalin and colloidal gold tests were negative. Apart from the raised serum bilirubin these tests were compatible with normal hepatic function. Serum cholesterol was 1,200 mg. per 100 ml. Urobilin and urobilinogen as well as a trace of bile were present in the urine. Stercobilin was present in the stools. A skin biopsy confirmed that the deposits in the subcutis were cholesterol.

No change in the clinical picture was observed during her stay in hospital. She was considered to be suffering from an incomplete or partial obstructive jaundice associated with generalized xanthomatosis. This was believed to be the primary abnormality and as such she was presented at the Royal Society of Medicine (Smythe and Dobbs, 1949).

The child died three months after discharge from hospital at the age of 2 years and 9 months. Just before death she became deeply jaundiced with a bilirubin of 13·6 mg. per 100 ml. Autopsy revealed a bilateral acute pyelonephritis as the immediate cause of death*. Xanthomatous deposits were found in the endocardium and the subintima of the great vessels, as well as on the posterior surface of the epiglottis and the epiglottic folds. The liver was enlarged and jaundiced. The gall bladder contained a moderate amount of brownish bile which could be easily expressed along the main cystic and hepatic ducts which appeared to be patent. The spleen was enlarged and firm but showed no definite abnormality.

The microscopy of the liver has been described in detail by Ahrens *et al.* (1951), and will be discussed later.

Case 2. S.P., female, was 5 years old in May, 1958. She was born of a healthy mother after a normal pregnancy and there have been no other siblings (1958). The father is not known. The child was delivered by forceps, weighed 6 lb. 2 oz. and was apparently healthy. Jaundice was noted on the fourth day of life and this rapidly increased in severity. The stools became pale and the urine dark. A congenital obstruction to the flow of bile was suspected, and a laparotomy was performed on the sixteenth day of life. At operation the gall bladder was found to be empty and deeply buried in the fissure. The cystic duct was traced to where the common bile duct should have been, but the latter could not be identified with certainty. There was no extrahepatic distension of the bile ducts and aspiration of the liver did not locate any collection of bile. An unfavourable prognosis was given. However, though the child remained thin and jaundiced her general condition did not deteriorate.

She was re-examined at the age of 8 months when her complexion was described as pale olive. Her serum bilirubin was 1·5 mg. per 100 ml., and stercobilin was identified in the stools. Since then there has been no increase in the degree of clinical jaundice and her general health has also remained relatively good.

She was admitted to The London Hospital in June, 1956, at the age of 3 years 1 month. She was then a stunted child, 27 lb. in weight and 30 inches in height. There was very slight generalized jaundice. The liver was enlarged, its edge was smooth, firm and palpable three and three-quarter inches below the costal margin. The tip of the spleen was just palpable. There was a systolic cardiac murmur audible over the praecordium.

The relevant investigations at this time were as follows: liver function tests: serum bilirubin, 4·5 mg. per 100 ml.; alkaline phosphatase, 54 units; thymol turbidity, 0·8 units; thymol flocculation, 0; zinc sulphate test, 3·5 units; serum proteins, 7 mg. per 100 ml. (albumin, 5·1; globulin, 1·9). Apart from the raised serum bilirubin and the slightly raised alkaline phosphatase these tests were compatible with normal hepatic function. Cholesterol was 1,600 mg. per 100 ml.; total lipids, 3,800 mg. per 100 ml.; and lipo-proteins, 1,300 mg. per 100 ml. The urine contained bilirubin, and urobilinogen within normal limits. Stercobilin was present in normal quantities in the stools. The bone age was within normal limits.

The child's general health remained good. She was cheerful and happy in spite of continued pruritus which caused a great deal of scratching. A sparse papular eruption first noted one month after admission was soon followed by the appearance of numerous yellow shiny xanthomatous deposits in the skin flexures and over the buttocks (Fig. 3). No skin biopsy was done. She grew two and a half inches within the course of nine months but failed to gain any significant amount of weight.

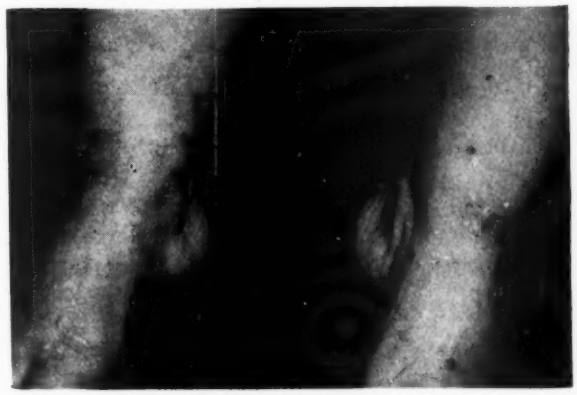


FIG. 3. Case 2. Skin xanthomata.

This clinical picture reminded us of Case 1, and of the histological description by Ahrens, to whom autopsy material had been sent. A tentative diagnosis of intrahepatic biliary atresia was made, and a drill biopsy of the liver was performed. This showed a histological pattern almost identical with that of Case 1, for a description of which the monograph by Ahrens and his colleagues should be consulted (Ahrens *et al.*, 1951)

* (Autopsy no. 5/42. General Hospital, Southend, Essex.)

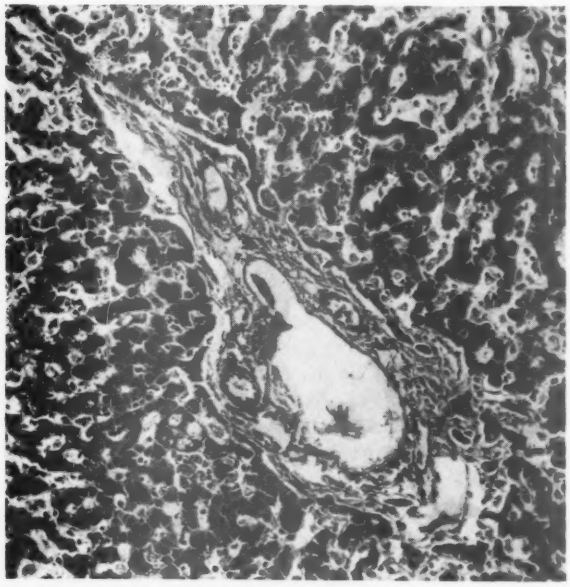


FIG. 4.—Case 1. Section of liver showing portal tract containing portal vein and hepatic artery but no bile duct. H. and E. × 110.

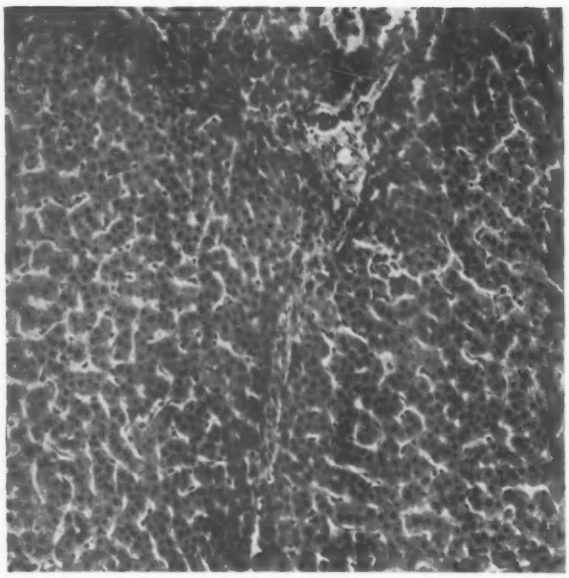


FIG. 5.—Case 2. Section of liver from biopsy specimen showing single thin fibrous band in otherwise normal parenchyma. H. and E. × 105.

(Figs. 4, 5 and 6). Briefly the most important and apparently essential abnormality in both cases was found in the portal tracts: portal veins and normal hepatic arteries were present but the accompanying bile ducts were absent. In contrast the intralobular canaliculi were present in both cases, and contained inspissated bile casts in Case 1 but not in Case 2. The portal tracts were infiltrated with small round cells in both cases, more marked in Case 1, in which a slight excess of extralobular fibrous tissue was also present. The liver cells looked normal. The Kupffer cells in Case 1 were large and contained lipoid material. The architecture of the lobules was still normal and there was no evidence of cirrhosis.

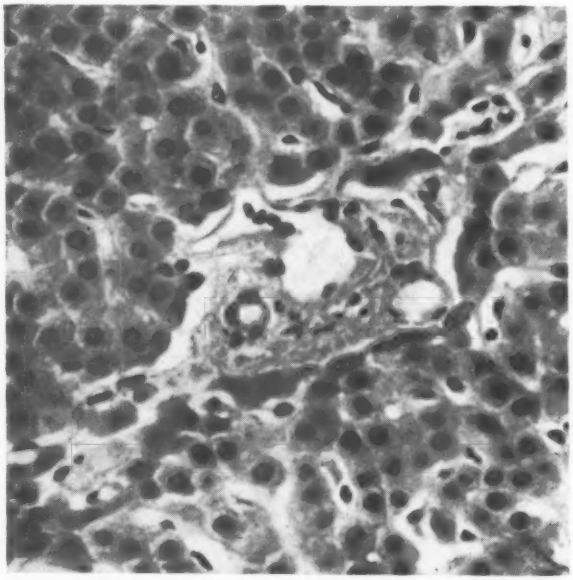


FIG. 6.—High power view of same section as Fig. 5 showing portal tract with absent bile duct. H. and E. × 325.

Discussion

Ahrens *et al.* (1951) were the first to describe this condition in detail. They reported two cases of their own as well as two others, one of which was Case 1 above. They also collected nine further cases from the literature which they thought comparable, though in seven of these the clinical and pathological details appear to us insufficient to be sure that they belong to the same group. The two remaining cases, however, Case 2 reported by Dahl-Iversen and Gormsen (1944), and the one reported by Sacrez, Fruhling and Rohmer (1946), are clearly the same condition on clinical as well as histological grounds. We have been able to find three more cases which have been fully described since then (MacMahon and Thannhauser, 1952; Moyson, Gillet and Richard, 1953; Sass-Kortsak, Bowden and Brown, 1956) and brief references to three others in which clinical details are not given (MacMahon and Thannhauser, 1952; Redo, 1954; Kiesewetter, Koop and Farquahr, 1955).

There are, therefore, now 10 well-documented cases of this condition, two male and eight female.

The important features of these 10 cases are summarized in Table 1. Four of the children, including Case 2 of this report, were alive and relatively well at the time of reporting. Two of them, the only two boys in the series, are known to have reached the ages of 10 and 12 respectively (MacMahon and Thannhauser, 1952; Harris, 1957). Apart from the infant who died at birth all these children have certain features in common: (1) They suffered from obstructive jaundice in the first week of life. As they lived on, their jaundice became less intense and bile pigment reappeared in the faeces. (2) The extrahepatic biliary system, either at laparotomy or at autopsy, was found to be patent in nine of the 10 patients. In one (Ahrens *et al.*, 1951: Case 3), although the gall-bladder was found to contain bile at autopsy, the cystic duct was patent for only 1 cm. and then became a thick fibrous cord which extended to the ampulla of Vater. The hepatic ducts in this case were not identified. (3) Elevation of the serum lipids was found in all seven cases in which this estimation was carried out. The serum cholesterol levels were often very high and well above 500 mg. per 100 ml. except in one case in which the readings varied between 212 and 300 mg. per 100 ml. between the ages of 7 weeks and 3 months at which age she died (Sass-Kortsak *et al.*, 1956). (4) Xanthomatous cutaneous deposits were present in all but four cases. The youngest recorded appearance of these was at the age of 1 year 3 months (Ahrens *et al.*, 1951: Case 3), and the oldest at approximately the age of 6 (McMahon and Thannhauser, 1952). In all these cases pruritus preceded the appearance of xanthomata by several months. (5) The microscopical changes of the liver in all cases showed essentially the same abnormalities as described above. These consisted of absence of the bile ducts in the portal tracts, slight infiltration of portal tracts with lymphocytes, plasma cells and polymorphs, normal looking liver cells and absence of any distortion of lobular architecture or significant increase of fibrous tissue in the portal tracts even in late stages of the disease.

The more frequent causes of neonatal obstructive jaundice differ both clinically and pathologically from this syndrome. In extrahepatic biliary atresia in which the site of obstruction may be anywhere between the portal tracts and the ampulla of Vater, the jaundice persists until the infant dies. During the neonatal period there is marked proliferation of perilobular bile ducts with gross dilatation in places of the larger bile ducts in the portal tracts and many of them are plugged by inspissated bile. Even in the early stages there is increase of fibrous tissue in the portal tracts which becomes very marked in those infants surviving more than a few months. The liver cells are often swollen and contain bile pigment. In the course of time true cirrhosis may ensue (Figs. 7 and 8).

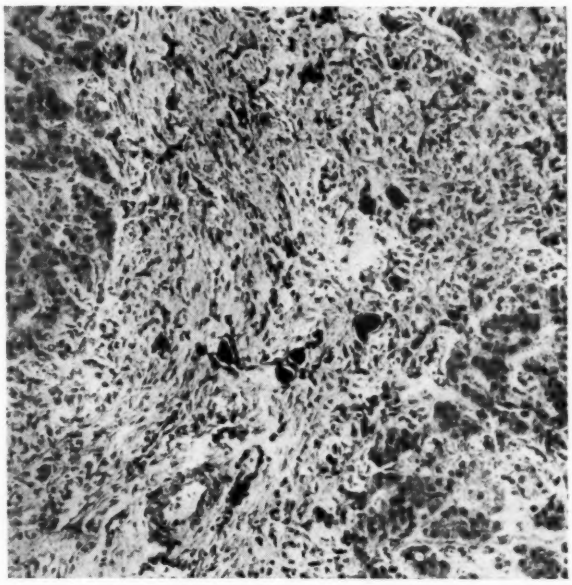


FIG. 7.—Section of post-mortem specimen of liver from patient with extrahepatic biliary atresia, showing wide fibrous tissue bands in portal region. Numerous portal bile ducts with inspissated bile casts. H. and E. × 105.

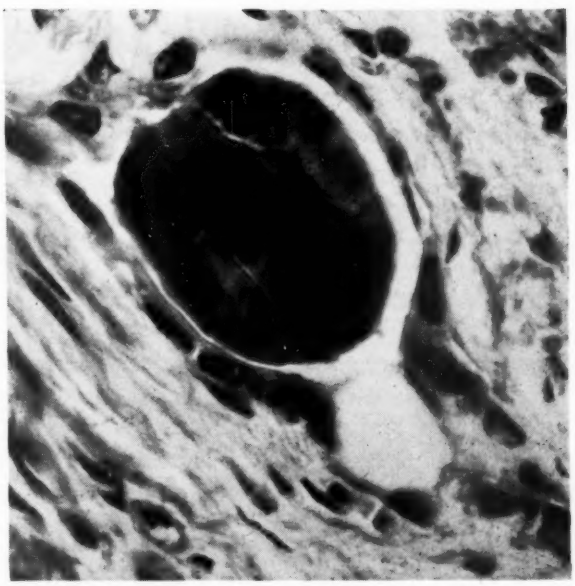


FIG. 8.—High power view of same case showing presence of portal bile duct surrounding inspissated bile cast. H. and E. × 830.

In neonatal hepatitis the jaundice may persist for a number of weeks but is followed in the majority

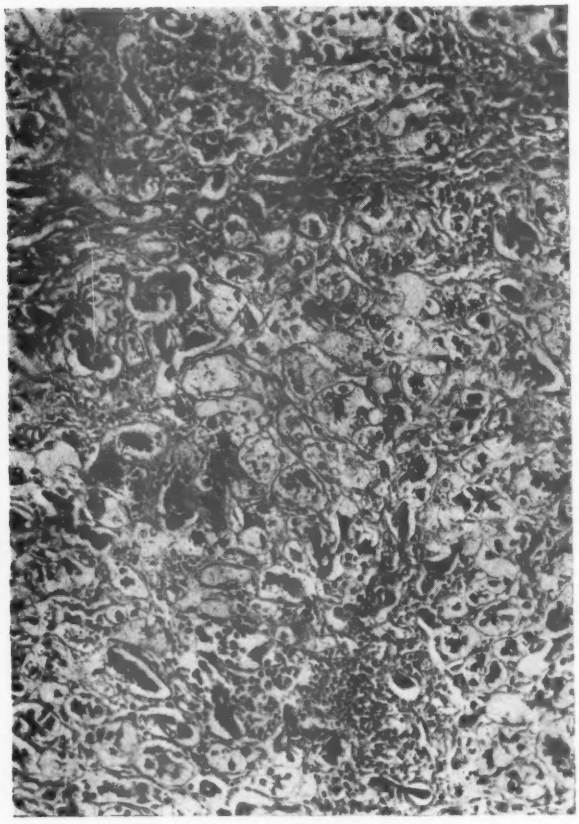


FIG. 9.—Section of post-mortem specimen of liver from child with neonatal hepatitis, showing large multinucleate parenchymal cells.

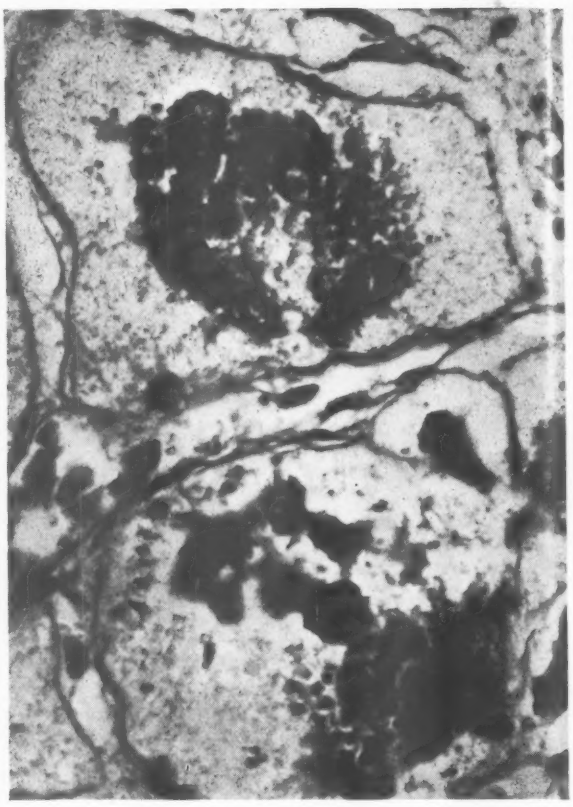


FIG. 10.—High power of same section.

of cases by a complete recovery. There is, however, a mortality rate of 20% and a further 10% of patients develop cirrhosis of the liver (Gellis, Craig and Hsia, 1954). The microscopical picture during the neonatal stage shows marked variation in the size of the liver cells, with distorted multinucleated giant cells scattered throughout the liver substance (Craig and Landing, 1952; Bodian and Newns, 1953). In

Author	Dahl-Iversen and Gormsen (1944)	Sacrez *et al.* (1946)	Case 1	Case 2
Age of reported onset of jaundice	Birth	8 d.	1 w.	2 d.
Age of appearance of xanthomata	—	—	1 yr. 9 mth.	3½ yr.
Age of first reported hyperlipaemia	—	—	1 yr.	3 yr. 9 m
Highest and lowest recorded serum cholesterol levels in mg./100 ml.	—	—	1,816 149	1,020 687
Age of onset of pruritus	—	—	1½ yr.	3 yr.
Age of reporting	Birth	2 yr. 7 mth.	3½ yr.	6½ yr.
Age of liver histology	Birth	2 yr. 7 mth.	1 yr. 1 mth.	3 yr. 9 m
Age of death	Birth	2 yr. 7 mth.	3 yr. 6 mth.	—
Cause of death	'Lethargy'	Meningitis	Liver failure	—
Extrahepatic biliary system	Normal	Normal	Normal	Normal

the chronic stage of the disease the lobular architecture is distorted by fibrous tissue and a true cirrhosis may follow (Figs. 9 and 10) (Bodian and Newns, 1953; Dible, Hunt, Pugh, Steingold and Wood, 1954).

In the bile-inspissation syndrome of Lightwood and Bodian (1946) prolonged haemolytic jaundice due to Rhesus incompatibility became complicated by biliary obstruction; this they showed histologically to be associated with inspissation of bile in the canaliculi.

A variety of other conditions occasionally cause liver damage associated with jaundice, pale stools and dark urine in the newborn. Inclusion-body disease was reviewed by France (1951); umbilical sepsis with generalized septicaemia, toxoplasmosis, congenital syphilis and herpes simplex, by Sherlock (1955). The clinical course of all these diseases is short and acute and totally unlike the condition under discussion.

It seems that in no other neonatal condition, particularly not in the later stages of either extrahepatic bile duct atresia or neonatal hepatitis, do hypercholesterolaemia or xanthomatosis occur. The association of liver disease with chronic jaundice and deposits in the skin has been known for more than a century (Addison and Gull, 1851). More recently Ahrens and others (Ahrens and Kunkel, 1949; MacMahon and Thannhauser, 1949; Ahrens, Payne, Kunkel, Eisenmenger and Blondheim, 1950), in their comprehensive monographs have fully discussed this relationship; briefly, elevation of the serum lipids is found in chronic biliary obstruction from any cause of sufficient duration provided liver cell function remains normal. When the serum cholesterol remains above a level of about 1,800 mg. per 100 ml. for longer than a few months, xanthomatous deposits begin to appear in the skin.

Aetiology and Treatment

Ahrens *et al.* (1951) consider the absence of the intrahepatic bile ducts to be a developmental anomaly and, indeed, the typical histological picture was seen in one newborn infant as well as in another 3 months of age. At present treatment is entirely symptomatic. Pruritus may be relieved by the administration of methyl testosterone (Lloyd-Thomas and Sherlock, 1952) and, in Case 2, stenediol, 10 mg. on alternate days, was tried with good effect. An attempt was made to lower the circulating lipids by giving a diet devoid of all animal and saturated vegetable fats (Bronte-Stewart, Antonis, Eales and Brock, 1956) for two periods of two months each and one of one month, with intervening periods of a month. The result was disappointing, there being neither appreciable reduction of the serum lipid levels nor any regression of the xanthomata.

Summary

Two cases of congenital absence of intrahepatic bile ducts are described.

Together with eight other similar cases from the literature, their clinical and pathological features are discussed and are contrasted with those of other causes of neonatal obstructive jaundice.

Though some of these other conditions appear very similar during the neonatal period, the clinical course of intrahepatic atresia is sufficiently characteristic during the next nine to 12 months for a diagnosis

Case 2	Case 3	MacMahon and Thannhauser (1952)	Moyson *et al.* (1953)	Sass-Kortsak *et al.* (1956)	Present paper Case 1†	Present paper Case 2
2 d.		8 d.	3 mth.	3 d.	2 d.	4 d.
3½ yr.	3 mth.	6 yr.	—	—	1 yr. 8 mth.	3 yr. 2 mth.
3 yr. 9 m	—	12 yr.	9 mth.	7 w.	2 yr. 6 mth.	3 yr. 1 mth.
1,020 687	—	1,686	300 212	922 362	1,200 1,081	1,600 500
3 yr.	1 mth.	Uncertain	—	—	5 mth.	3 yr. 1 mth.
6½ yr.	yr.	10 yr.	11¼ mth.	7 w.	2½ yr.	3 yr. 1 mth.
3 yr. 9 m	3 mth.	10 yr.	11½ mth.	3½ mth.	2 yr. 9 mth.	3 yr. 3 mth.
—	3 mth.	—	—	3 yr. 6 mth.	2 yr. 9 mth.	—
—	ryngitis, liver failure	—	—	Staphylococcal pneumonia	Pyelonephritis	—
Normal	otic cystic and common bile ducts	Normal	Normal	Normal	Normal	? Normal

Ahrens *et al.* (1951).

to be made, whilst probably at any time a liver biopsy will be pathognomonic.

We would like to express our thanks to Dr. Kenneth Tallerman for permission to allow us to report our second case, to Dr. Preedy for performing the liver biopsy and also to Dr. Weinbren for his histological reports.

References

Addison, T. and Gull, W. (1851). *Guy's Hosp. Rep.*, **7**, 265.
Ahrens, E. H. Jr., Harris, R. C. and MacMahon, H. E. (1951). *Pediatrics*, **8**, 628.
—— and Kunkel, H. G. (1949). *J. clin. Invest.*, **28**, 1565.
——, Payne, M. A., Kunkel, H. G., Eisenmenger, W. J. and Blondheim, S. H. (1950). *Medicine* (*Baltimore*), **29**, 299.
Bodian, M. and Newns, G. H. (1953). *Arch. franç. Pédiat.*, **10**, 169.
Bronte-Stewart, B., Antonis, A., Eales, L. and Brock, J. F. (1956). *Lancet*, **1**, 521.
Craig, J. M. and Landing, B. H. (1952). *Arch. Path.* (*Chicago*), **54**, 321.
Dahl-Iversen, E. and Gormsen, H. (1944). *Acta chir. scand.*, **89**, 333.
Dible, J. H., Hunt, W. E., Pugh, V. W., Steingold, L. and Wood, J. H. F. (1954). *J. Path. Bact.*, **67**, 195.
France, N. E. (1951). *Arch. Dis. Childh.*, **26**, 588.
Gellis, S. S., Craig, J. M. and Hsia, D. Y. Y. (1954). *Amer. J. Dis Child.*, **88**, 285.
Harris, R. C. (1957). Personal Communication.
Kiesewetter, W. B., Koop, C. E. and Farquahr, J. D. (1955). *Pediatrics* **15**, 149.
Lightwood, R. and Bodian, M. (1946). *Arch. Dis. Childh.*, **21**, 209.
Lloyd-Thomas, H. G. L. and Sherlock, S. (1952). *Brit. med. J.*, **2**, 1289.
MacMahon, H. E. and Thannhauser, S. J. (1949). *Ann. intern. Med.*, **30**, 121.
——, —— (1952). *Gastroenterology*, **21**, 488.
Moyson, F., Gillet, P. and Richard, J. (1953). *Helv. paediat. Acta*, **8**, 281.
Redo, S. F., (1954). *Arch. Surg.* (*Chicago*), **69**, 886.
Sacrez, R., Fruhling, L. and Rohmer, J. A. (1946). *Arch. franç. Pédiat.*, **3**, 78.
Sass-Kortsak, A., Bowden, D. H. and Brown, R. J. K. (1956). *Pediatrics*, **17**, 383.
Sherlock, S. (1955). *Diseases of the Liver and Biliary System.* Oxford.
Smythe, P. M. and Dobbs, R. H. (1949). *Proc. roy. Soc. Med.*, **42**, 86.

REPLACEMENT TRANSFUSION AS A MEANS OF PREVENTING KERNIKTERUS OF PREMATURITY

BY

V. MARY CROSSE, PATRICIA G. WALLIS and ANNA M. WALSH

From Sorrento Maternity Hospital, Birmingham

(RECEIVED FOR PUBLICATION FEBRUARY 25, 1958)

The possibility of premature babies developing kernikterus from jaundice not due to haemolytic disease is now generally recognized (Aidin, Corner and Tovey, 1950; Zuelzer and Mudgett, 1950; Hsia, Allen, Diamond and Gellis, 1953; Billing, Cole and Lathe, 1954; Crosse, Meyer and Gerrard, 1955; Meyer, 1956).

In haemolytic disease kernikterus has been practically eliminated by the use of repeat replacement transfusion to wash out the excess of bilirubin, and this form of treatment therefore seems to be indicated for the prevention of kernikterus due to prematurity.

Since the beginning of July, 1955, bilirubin levels have been estimated each morning (and when necessary in the evening also) in all premature babies showing definite clinical jaundice during the first eight days of life; and replacement transfusion has been performed in each case in which the level reached 18-20 mg.% during this period or was rising so rapidly that it would probably have reached this level before the next morning. Haemolytic disease has been proved or disproved in each case by full examination of the blood of both mother and baby. The transfused babies have been followed up carefully to assess any damage (however small) which might have resulted from the jaundice or from the transfusion.

Material

The 1,320 babies studied were the total number of admissions to the three premature baby units under our care during the two-year period from July 1, 1955, to June 30, 1957.

The degree of jaundice was roughly estimated by blanching the skin, either by stretching or by pressure. If examined by daylight it soon became possible to decide whether the level of bilirubin had reached approximately 10 mg.% or not. If it appeared to have reached this level, blood was taken for bilirubin estimation and to exclude haemolytic disease. In two of the units blood was taken by femoral puncture, and in one by multiple heel prick.

Results

Number of Babies who Required Transfusion. Table 1 shows all premature babies admitted to the three premature baby units during the two years under investigation, and the number who required replacement transfusion for hyperbilirubinaemia not due to haemolytic disease. The 1,320 babies are divided into three birthweight groups: group A includes all babies up to 1,500 g. at birth, group B babies from 1,500-2,000 g., and group C babies from 2,000-2,500 g.

With the exception of group A, the percentage of babies requiring transfusion diminished as the birthweight increased. Because many babies weighing less than 1,500 g. die before they can develop hyperbilirubinaemia, the transfused babies are also given as a percentage of the babies at risk (babies alive at 48 hours) but even when this is done group A still shows the smallest percentage of babies transfused. The reason for this is difficult to understand unless it was due to the small numbers involved. It is of interest that this discrepancy was not present among the babies treated in Sorrento premature baby unit which deals with the highest proportion of small babies. In Sorrento during the past two and a half years, eight out of 207 babies weighing less than 1,500 g. at birth (group A) were transfused (3·9%). If only the 99 babies at risk (alive at 48 hours) are considered, 8·1% were transfused. For comparison, 8·5% of the babies at risk were transfused in group B, and 7·5% in group C. If by chance, one more baby in group A had been transfused, this would have raised the percentage in this group to 9·1%.

Of the total 1,320 premature babies admitted, 92 (8·4%) required replacement transfusion for hyperbilirubinaemia not due to haemolytic disease. It is of interest to find that the five cases of kernikterus which occurred during this series were all in group B.

Number of Babies who Required more than One Transfusion. If, after the first transfusion, the level of bilirubin rose again to dangerous levels, the same

TABLE 1
BABIES REQUIRING REPLACEMENT TRANSFUSIONS

Birth Weight	Total Admissions	Babies at Risk (alive at 48 hr.)	Babies Transfused		
			No.	% of total	% of babies at risk
Group A (Up to 1,500 g.) ..	262	137	8	3·1	5·8
Group B (1,500–2,000 g.) ..	564	499	49	8·7	9·8
Group C (2,000–2,500 g.) ..	494	464	35	7·1	7·5
Total	1,320	1,100	92	7·0	8·4

criteria as before were used as indications for a repeat transfusion.

Table 2 shows the number of transfusions required by each affected baby in each of the three birthweight groups. The proportions of transfused babies requiring more than one transfusion show the same variations as in Table 1 but of course the numbers concerned are extremely small.

Of all transfused babies, 19·6% required more than one transfusion to keep the bilirubin below a dangerous level.

All five babies who later showed signs suggestive of kernikterus required more than one replacement (one baby required four, one required three and the remaining three babies two each).

Mortality Due to Transfusion. There were two deaths among the transfused babies but only one was due to transfusion. This baby weighed 3 lb. 4 oz. at birth. The transfusion was technically easy and 250 ml. were exchanged but unfortunately no deficit was left. The baby collapsed and died five minutes after the completion of the transfusion. An autopsy showed that death was due to heart failure. Since this occurrence a deficit of 20-40 ml. has always been left.

The second death occurred in a baby which weighed 4 lb. 11 oz. at birth. This baby's mother had severe pre-eclampsia. The condition of the baby was extremely poor at birth and continued so. Jaundice developed rapidly and on the third day a replacement transfusion became necessary. The baby improved slightly after the transfusion but 12 hours later collapsed suddenly and died. An autopsy showed that death was due to gross atelectasis and the transfusion was not believed to have contributed to the death.

Babies in whom a Satisfactory Replacement was not Obtained. A replacement was called unsatisfactory if less than 80 ml./lb. (176 ml./Kg.) were exchanged.

Among the 92 first transfusions there was a failure to obtain a satisfactory replacement in three cases: this was due to spasm of the umbilical vein in two cases and failure to cannulate the umbilical vein in one.

There were also three failures among the 18 repeat transfusions. In each case the umbilical vein had been ligated after the first transfusion, and re-cannulation of the umbilical vein was impossible. In two of the three cases, the saphenous route was not attempted; in the third it was attempted but failed.

One baby comes into both these groups because the first transfusion was incomplete and the repeat transfusion failed. Five babies are therefore concerned, and two of these five babies developed kernikterus.

All six unsatisfactory replacements occurred during the early part of the period under review, and with our present technique failure should be rare. When spasm of the umbilical vein occurs, the replacement is now abandoned for one or two hours, after which time the spasm has usually relaxed. If it has not done so after this time the saphenous route is used. Repeat transfusions are now made easier by

TABLE 2
NUMBER OF TRANSFUSIONS REQUIRED

Birth weight	Babies Transfused	Transfused Babies				%Requiring more than one Transfusion
		No. of transfusions				
		One	Two	Three	Four	
Group A (Up to 1,500 g.) ..	8	7	1	—	—	12·5
Group B (1,500–2,000 g.) ..	49	38	9	1	1	22·4
Group C (2,000–2,500 g.) ..	35	29	4	2	—	17·1
Total	92	74 (80·4%)	14 (15·2%)	3 (3·3%)	1 (1·1%)	19·6

leaving the catheter *in situ* for several days in case a further transfusion should become necessary.

Age at First Transfusion. Fig. 1 shows the age at first transfusion for each of the three birthweight groups separately, and also for all cases together.

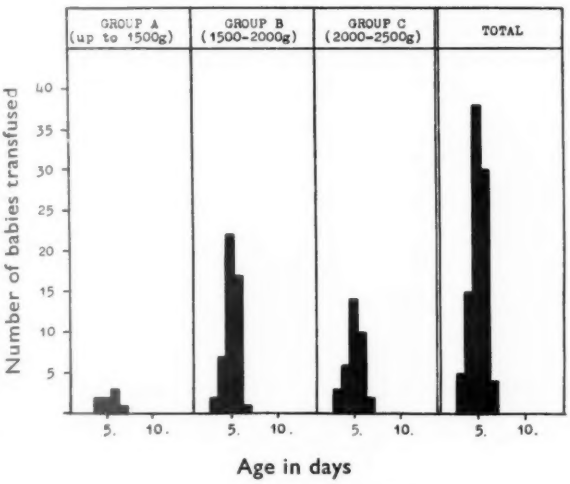


FIG. 1.—Age at first transfusion (92 babies).

In group A the first transfusion was performed between the ages of 3 days and 7 days, with the maximum incidence during the sixth day of life. In group B and C the first transfusion was performed between the ages of 2 days and 7 days and the maximum incidence was during the fifth day of life.

Of all 92 transfusions, five (5·4%) were undertaken on the third day of life, 15 (16·3%) on the fourth day, 38 (41·3%) on the fifth day, 30 (32·6%) on the sixth day, and four (4·4%) on the seventh day.

Of the five babies who developed kernikterus, the first transfusion was done on the third day in one case, on the fourth day in two cases, and on the fifth day in two cases.

Levels of bilirubin at which the decision was made to replace. (115 transfusions.) Fig. 2 shows these levels for each of the three birthweight groups separately, and for all cases together.

For 53 transfusions (46·1%) the decision was taken when the level of bilirubin was between 17 and 20 mg.%. In three of the four cases (3·5%) in which the decisions were made at lower levels, the jaundice was increasing so rapidly that it was not considered safe to leave the babies until the following morning; and in one case the reported level was believed to be incorrect because of the clinical severity of the jaundice.

For 58 transfusions (50·4%) the decision was made at levels over 20 mg.%. In the light of present knowledge this was too late because in all five babies who developed kernikterus, the decision to transfuse was made at levels over 20 mg.%. The decision to transfuse was made at levels over 20 mg.% for three out of nine transfusions (33·3%) in group A, for 32 out of 63 transfusions (50·1%) in group B, and for 23 out of 43 transfusions (53·5%) in group C.

When the decision to transfuse was taken at levels higher than 20 mg.%, this was usually due to lack of experience in judging the depth of jaundice. In some

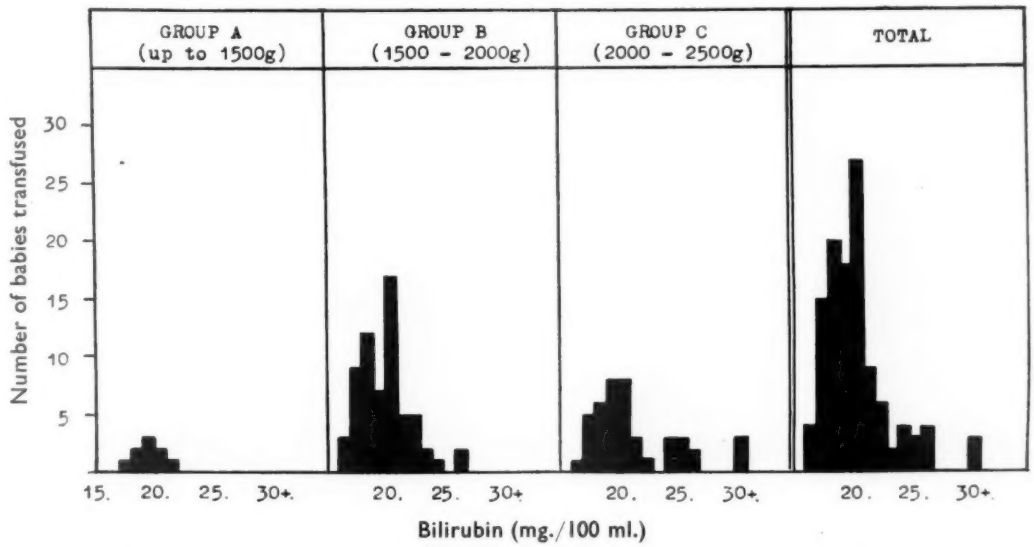


FIG. 2.—Level of serum bilirubin at which decision was taken to transfuse (115 transfusions).

cases the bilirubin level was first estimated when the critical level had already been reached; and in others the rate of increase in the depth of jaundice was not appreciated. It has been found that, with experience, the serum bilirubin level can be assessed clinically up to about 10-12 mg.%, but above that level it is impossible to judge the levels at all accurately clinically, and bilirubin estimations are now made much more frequently.

In the early months of the investigation different serum bilirubin results were frequently obtained by the various laboratories on the same blood. It was felt that the indications must be definite before embarking on what seemed a major operation, but as confidence in the safety of replacement transfusion was gained, and as the laboratory technique became more standardized, there was less hesitation in deciding to replace at lower and safer levels.

Highest Serum Bilirubin Levels Reached by Babies. Fig. 3 shows the highest bilirubin levels reached by babies in each of the three birthweight groups separately, and by all babies together.

In 29 (31·5%) of the 92 transfused babies the bilirubin level was kept below 20 mg.%; in 39 (42·4%) it rose to 20-22 mg.%, in 21 (22·8%) it rose to 22-27 mg.% and in three (3·3%) it rose above 30 mg.%. A rise to levels between 20 mg.% and 27 mg.% could be explained in each case by lack of experience either in judging the degree of the jaundice or in appreciating the rate of increase.

As regards the three babies in whom the bilirubin level rose to 30 mg.% or more, the following remarks may be of interest:

BABY R. (5 lb. 6 oz.) The bilirubin level reached 20 mg.% by the fourth day, but due to some misunderstanding the baby was not transfused. The level on the fifth day had risen to 30 mg.% and replacement transfusion was undertaken immediately. Luckily this child showed no signs of kernikterus and has developed normally.

BABY B. (4 lb. 1 oz.) This baby developed kernikterus and particulars are given in the section on the follow-up of all transfused babies.

BABY S. (5 lb.) This baby was slightly jaundiced on the first day and by the second day the bilirubin level had reached 14·6 mg.%. The level was not estimated that evening because the jaundice was not believed to have deepened. However the next morning the level was reported as 30 mg.% and an immediate replacement was performed. The child showed no signs of kernikterus and has developed normally.

These three babies were born during the first six months of the period under review. Bilirubin levels are now taken more frequently and such high levels are avoided.

The five babies who developed kernikterus were all in group B, and in each case the bilirubin level rose to 22 mg.% or more (two rose to 22 mg.%, two to 23 mg.% and one to more than 30 mg.%).

It is of interest that none of the 68 babies with levels below 22 mg.% developed kernikterus, while four of the 21 (19·2%) with levels of 22-27 mg.%, and one of the three (33·3%) with levels over 30 mg.% developed this complication.

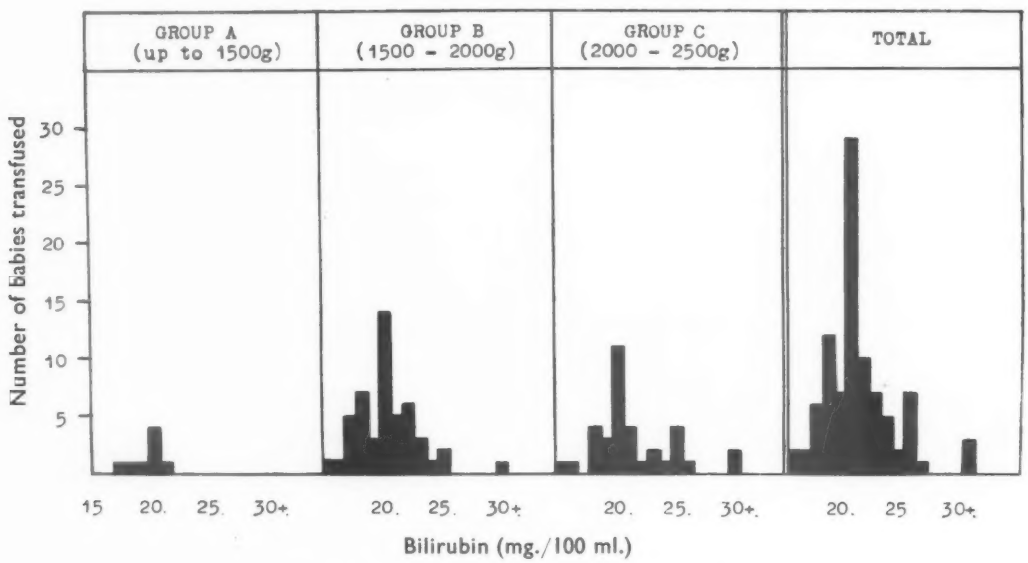


FIG. 3.—Highest serum bilirubin levels reached (92 babies).

No baby over 2,000 g. developed kernikterus. When babies under 2,000 g. are considered by themselves, four out of the 12 (33·3%) with bilirubin levels of 22-27 mg.% and the only one with a bilirubin level over 30 mg.% developed kernikterus. This was in spite of the fact that these high bilirubin levels were present for a relatively short time, except in the case of baby B.

Reduction in Bilirubin Level Achieved by Transfusion. It is impossible to give complete figures for this because technical difficulties often prevented the collection of all the required samples of blood. However, in cases in which the necessary samples were obtained, the reduction in the bilirubin level during transfusion usually varied from 45%-65%.

Follow-up of Transfused Babies. A great effort has been made to follow-up the 92 transfused babies. This has been difficult owing to the wide geographical area from which the units draw their cases. It was intended that each baby should be seen at three-monthly intervals until the age of at least 1 year. Actually 83 of the 90 surviving transfused babies have been followed to the age of 1 year, and one to the age of 9 months. The remaining six have moved to unknown addresses and all efforts to trace them have failed. There is, however, no reason to believe that any of these six babies are abnormal; when last seen by the doctor or health visitor they were considered normal.

The following five babies have developed signs which are probably due to kernikterus:

BABY G. (3 lb. 7 oz.) On the fourth day the bilirubin level rose from 16 mg.% in the morning to 20 mg.% in the evening; then unfortunately there was a delay of five hours before the baby was transfused. By this time the jaundice had increased (bilirubin 22 mg.%) and early signs of kernikterus had developed, i.e. head retraction, eye rolling and periods of apnoea during which cyanosis developed. This child is now spastic and possibly retarded, but is not deaf.

BABY K. (4 lb.) A transfusion was given on the fifth day when the bilirubin level was 21 mg.%, but a complete exchange was not achieved due to spasm of the umbilical vein after 100 ml. had been exchanged. The catheter was removed and the vein ligated. The following day the bilirubin level rose to 23 mg.%, but the umbilical vein could not be cannulated and the femoral route was not attempted. The bilirubin level began to fall the next day. No head retraction or other signs of kernikterus were seen and there were also no signs of birth injury or asphyxia during early life. The child is now mildly spastic, very emotional and probably slightly retarded, but is not deaf. In spite of the apparent absence of signs of kernikterus in the early days, this baby must be included because of the history of hyperbilirubinaemia.

BABY B. (4 lb. 1 oz.) This child was transfused on the third day (bilirubin 20 mg.%) and again on the sixth day (bilirubin 22 mg.%), but this time the umbilical vein went into spasm after 60 ml. had been exchanged. No further attempt was made because it was felt (wrongly) that the level of bilirubin would probably fall after this age. In fact the baby became more deeply jaundiced and signs of kernikterus developed on the ninth day when the bilirubin level was found to have reached 38 mg.%. This child is now definitely spastic and retarded, is having convulsions and probably has a hearing defect.

BABY C. (3 lb. 8 oz.) This child was transfused on the third day (bilirubin 18 mg.%). By the fourth day the bilirubin level had risen again to 20 mg.% but the baby was not transfused until six hours later when the bilirubin level had reached 22 mg.%. A third transfusion was carried out on the fifth day (bilirubin 20 mg.%). On the sixth day the bilirubin level had risen again to 18·4 mg.% but transfusion was not performed. By the seventh morning the baby had developed head retraction and the bilirubin level was again 22 mg.%. In spite of the head retraction a fourth transfusion was undertaken (with the hope of limiting the degree of brain damage) and after this the level of bilirubin fell steadily. This child now shows no spasticity but has been late in reaching all his mile-stones. There is a tendency to athetosis and there also appears to be some hearing defect.

BABY H. (3 lb. 15 oz.) This child was in a poor condition from birth. He had marked atelectasis and an enlarged liver, he also showed signs of cerebral irritation; he was not expected to survive. The first transfusion was undertaken on the fourth day (bilirubin 21 mg.%), a second on the fifth day (bilirubin 23 mg.%) and a third on the seventh day (bilirubin 20 mg.%). After this the level of bilirubin gradually fell. There were no definite signs of kernikterus at any time, but the general condition was very poor throughout the first week of life. This child is now spastic and probably retarded, but is not deaf. It is possible that this child's disability was the result of birth asphyxia, but he is included as a probable case of kernikterus because the bilirubin was allowed to rise to 23 mg.% on the fifth day.

From a study of these cases, it appears that all five were preventable, and much has been learnt from these failures.

A better realization of the rapidity of the rise in the level of the bilirubin by more frequent estimations during the critical period, thus enabling transfusions to be undertaken at lower levels, would have been helpful in all five cases.

The realization that the bilirubin could still rise to dangerous levels after the sixth day of life would have helped Baby B.

A reduction in the time between taking the actual blood sample and starting the transfusion might have saved babies S and C.

Better technique to avoid incomplete exchanges might have helped babies K and B, i.e. a period of rest to allow venous spasm to relax, leaving the

catheter *in situ* in case further transfusions become necessary, and the use of the saphenous route if the umbilical route fails.

Discussion

In order to assess the value of replacement transfusion in hyperbilirubinaemia not due to haemolytic disease, it is necessary to know what proportion of the premature babies admitted to our units would have developed kernikterus without such preventive treatment.

During the two years 1953 and 1954, the excessive use of vitamin K increased the number of cases of kernikterus occurring in our units (Crosse *et al.*, 1955), but before this unhappy episode, i.e. during the eight-year period 1945-1952, 1·08% of all admissions developed kernikterus, and approximately 70% of these babies died.

If this incidence (1·08%) is applied to the 1,320 admissions during the two years under review the expected number of cases of kernikterus would be 14. Of these, nine or 10 would have died, and four or five would have survived but suffered cerebral palsy. Instead, one baby has died (from transfusion) and five babies have developed cerebral palsy, two of whom are only slightly affected. If certain failures in diagnosis and technique had not occurred, these five cases might have been prevented. (Unfortunately the bilirubin level was allowed to rise above 22 mg.% in each case.)

Until some better method of preventing this important and dangerous complication of prematurity becomes available (e.g. conversion of the lethal indirect-acting into the harmless direct-acting bilirubin; or reduction of the rate of breakdown of the red blood cells so that the immature liver can cope with the reduced amount of bilirubin) replacement transfusion appears to be the only way of coping with the situation.

To avoid failures such as those described it is obviously necessary to keep the bilirubin level below 20-22 mg.% at all times, and this entails an exacting regime. In all hospitals where premature babies are treated, it is necessary to have a sufficient number of experienced nurses and doctors who can decide when the bilirubin level is approaching 10-12 mg.% and promptly take blood samples for laboratory estimation. Accurate estimations must be made on these samples, and the bilirubin level promptly reported. If the level is over 18 mg.% replacement should be performed with as little delay as possible. If the bilirubin level is rising rapidly a decision to replace may be made at a lower level, especially if the decision has to be made in the evening, with a long night ahead and the difficulty of assessing the degree of jaundice in artificial light and the reduction of laboratory facilities. In order to have some idea of the rate of rise in the level of bilirubin, the first estimation should not be left too late.

Full cooperation with the blood transfusion service is necessary to avoid undue delay between deciding to transfuse and performing the transfusion.

Medical staff with experience in replacement transfusion must be available at all hours of the day and night, and two assistants (nurses or medical students) should also be available.

Summary

The development of jaundice has been carefully observed in 1,320 premature babies admitted to three premature baby units during a period of two years, and exchange transfusions have been undertaken in 92 babies (8·4%) who developed hyperbilirubinaemia not due to haemolytic disease.

Of the transfused babies, 19·6% required more than one transfusion.

There were two deaths among the 92 babies transfused (115 transfusions), but one of these deaths could not be attributed either to the transfusion or to kernikterus.

The highest bilirubin level reached was less than 20 mg.% in 31·5%, 20-22 mg.% in 42·4%, 22-27 mg.% in 22·8%, and over 30 mg.% in 3·3%. No baby with a bilirubin level below 22 mg.% developed kernikterus, but 19·1% of those with levels of 22-27 mg.%, and 33·3% of those with levels over 30 mg.% developed this complication.

Of the 92 transfused babies five later showed signs which were probably due to kernikterus.

Until some better way has been found to prevent or treat hyperbilirubinaemia not due to haemolytic disease, it seems that replacement transfusion is the best way of preventing kernikterus.

We are very grateful to Dr. T. C. Meyer, Dr. Joan Angus, Dr. Frances Thompson and Dr. Daphne Hall, who performed many of the transfusions; to Dr. A. H. Henley for technical advice; to the laboratory staffs of Little Bromwich General Hospital, Sorrento Maternity Hospital and Marston Green Maternity Hospital; to Dr. W. Weiner and the staff of the Blood Transfusion Service; to Dr. H. S. Baar and Dr. F. E. D. Griffiths for the two autopsies; and to the Sisters and nursing staff of the three premature baby units without whose help this work could not have been undertaken.

References

Aidin, R., Corner, B. and Tovey, G. (1950). *Lancet*, **1**, 1153.
Billing, B. H., Cole, P. G. and Lathe, G. H. (1954). *Brit. med. J.*, **2**, 1263.
Crosse, V. M., Meyer, T. C. and Gerrard, J. W. (1955). *Arch. Dis. Childh.*, **30**, 501.
Hsia, Y. H., Allen, F. H., Diamond, L. K. and Gellis, S. S. (1953). *J. Pediat.*, **42**, 277.
Meyer, T. C. (1956). *Arch. Dis. Childh.*, **31**, 75.
Zuelzer, W. W. and Mudgett, R. T. (1950). *Pediatrics*, **6**, 452.

SERUM TRANSAMINASE VARIATIONS IN CHILDHOOD

BY

PAOLO TOLENTINO and MARCELLA ROSSI

From the Departments of Infectious Diseases and Paediatrics, University of Genoa

(RECEIVED FOR PUBLICATION MARCH 10, 1958)

The study of serum transaminases has recently entered clinical practice. In December, 1954, Wróblewsky and La Due demonstrated an increase of glutamic-oxalacetic (GOT) transaminase in the serum of patients suffering from various liver diseases and in carbon tetrachloride intoxication. In 1955, de Ritis, Coltorti and Giusti demonstrated an increase of both aspartic-ketoglutaric (GOT) and alanine-ketoglutaric (GPT) transaminases in the serum of patients with infectious hepatitis. This increase was accompanied by a remarkable inversion of the ratio between aspartic-ketoglutaric (GOT) and alanine-ketoglutaric activity (GPT), $(\frac{GOT}{GPT},)$ which stands above unity in healthy people and notably below in infectious hepatitis. While the increase of serum transaminase is generally ascribed to extensive necrosis of the hepatic cells and the consequent passage into the blood of cellular enzymes, the inversion of the ratio has not yet been satisfactorily explained.

A series of clinical and experimental observations made during the last two years has enabled us to reach some interesting conclusions. Our clinical researches concerned about 100 cases of acute infectious diseases, including infectious hepatitis, rheumatic fever, measles, scarlet fever, whooping cough, chickenpox, infectious mononucleosis, mumps and poliomyelitis. In some of the above-mentioned diseases multiplication of the causal agent in the liver during the incubation stage takes place, and liver damage is frequently observed at needle-biopsy.

In estimating the serum transaminases we used the method of Tonhazy, White and Umbreit (1950) reading with Pulfrich's photometer, filter S 53. The results are set out in Figs. 1, 2 and 3, the values being expressed in micromoles of pyruvic acid.

These figures show that only in infectious hepatitis, from virus A or B, is there a definite increase of both transaminases accompanied by the characteristic inversion of the ratio. This specific finding is probably related to the extensive liver

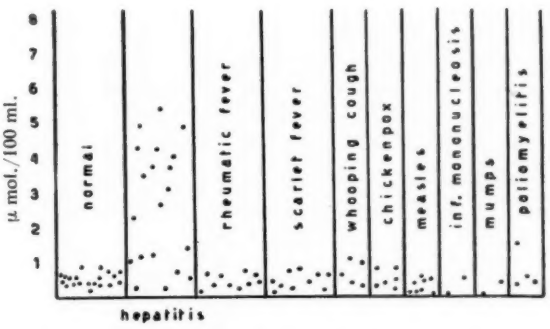


FIG. 1.—Serum aspartic-ketoglutaric (GOT) transaminase.

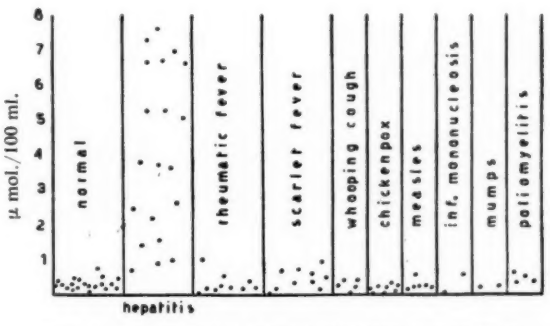


FIG. 2.—Serum alanine-ketoglutaric (GPT) transaminase.

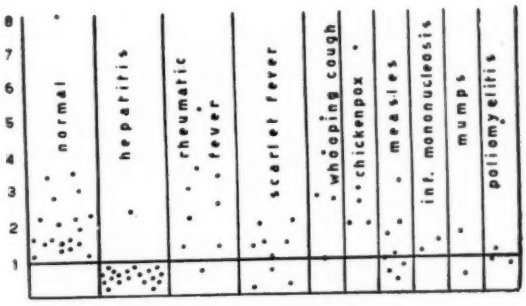


FIG. 3. $\frac{GOT}{GPT}$ ratio in some infectious diseases.

necrosis that is present only in this disease. However, we found the ratio inverted without a considerable increase of transaminase in a certain percentage of cases in other infectious diseases; we never found inversion in healthy subjects (Tolentino and Rossi, 1957a).

In numerous cases of hepatitis we estimated the serum transaminases throughout the course of the disease and observed that the values decreased with clinical improvement and rose again during relapses. The last pathological finding to disappear was the inversion of the GOT/GPT ratio.

In some cases we were also fortunate enough to be able to show that the increase in serum transaminases occurred very early, appearing about a month before the clinical manifestations. We observed this in children from a school, who were in contact with hepatitis patients. Fig. 4 charts the course of one such case and demonstrates that the pathological increase of transaminases, with inversion of the ratio, appeared as early as 36 days before fever and jaundice. The estimation of transaminases is, therefore, a valuable aid in detecting cases of hepatitis just at the beginning of the incubation period, with obvious prophylactic advantages. Thus it should be used routinely in blood donors in order to eliminate those with pathological values (Tolentino and Rossi, 1957b).

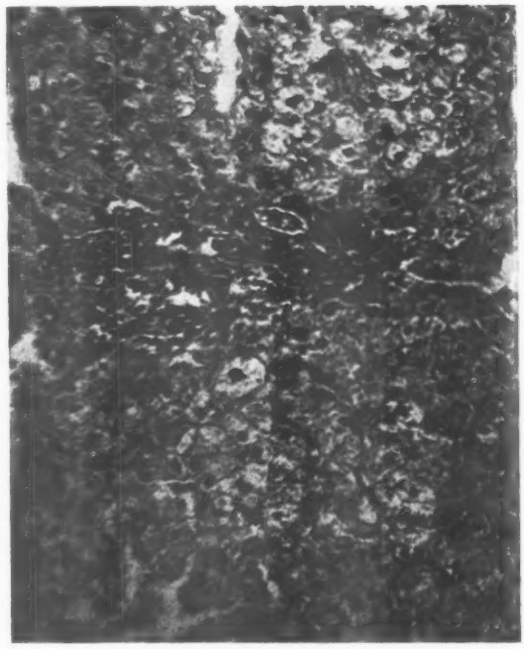


FIG. 5.—Needle-biopsy 30 days before jaundice (infectious hepatitis). Hydropic swelling of liver cells and inflammatory portal inflammation. H. and E. × 130.

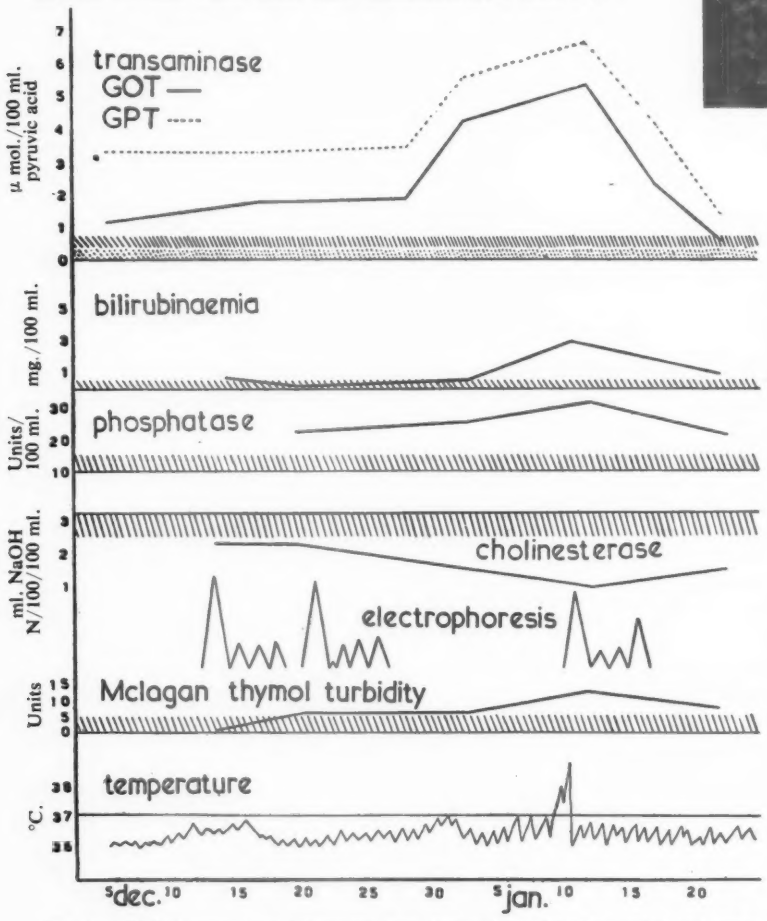


FIG. 4.—Clinical course and laboratory data during the incubation period and acute phase of a case of infectious hepatitis. Shading=normal values.

Methods: *Transaminase:* Tonhazy-White-Umbreit. *Bilirubinaemia:* Jendrassik Czike. *Phosphatase:* King-Armstrong. *Cholinesterase:* Stedman-Lucas. Electrophoresis on paper.

Since at the beginning of the incubation period there is sufficient necrotic damage of the hepatic cells to induce an increase of transaminases, and to be manifest at biopsy (as demonstrated in one case in Fig. 5), it seems that even at this early stage the virus is exerting its injurious action upon the liver. The unusually long duration of the incubation stage could be due to a peculiar slowness of virus multiplication, and clinical signs would appear only when a sufficient portion of tissue had been destroyed.

As has been mentioned above a dissociation exists in some clinical cases between increase of the

transaminases and inversion of the ratio: on the one hand some infectious diseases show an inversion of the GOT/GPT ratio without an increase of values, while on the other hand obstructive (as opposed to infective) jaundice demonstrates increased values without inversion (cases of obstructive jaundice of the newborn) (Kove, Goldstein and Wróblewski, 1957; some cases of ours). We sought an explanation of these phenomena in animal experiments.

This research gave the following results:

(1) In guinea pigs bile-duct ligature produced after only one hour a very quick and remarkable increase (about 10 times) of aspartic-ketoglutaric (GOT) transaminase and a smaller increase of alanine-ketoglutaric (GPT) transaminase; the normal ratio (Fig. 6) was therefore maintained.

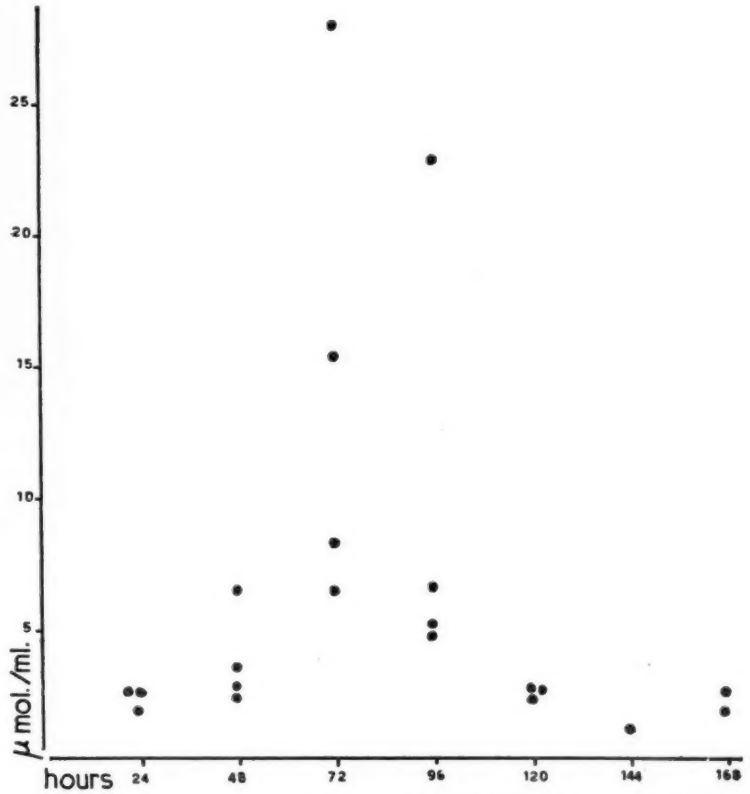


FIG. 7.—Serum transaminase (aspartic-ketoglutaric (GOT)) in mice inoculated with sub-lethal doses of mouse hepatitis virus (MHV_3).

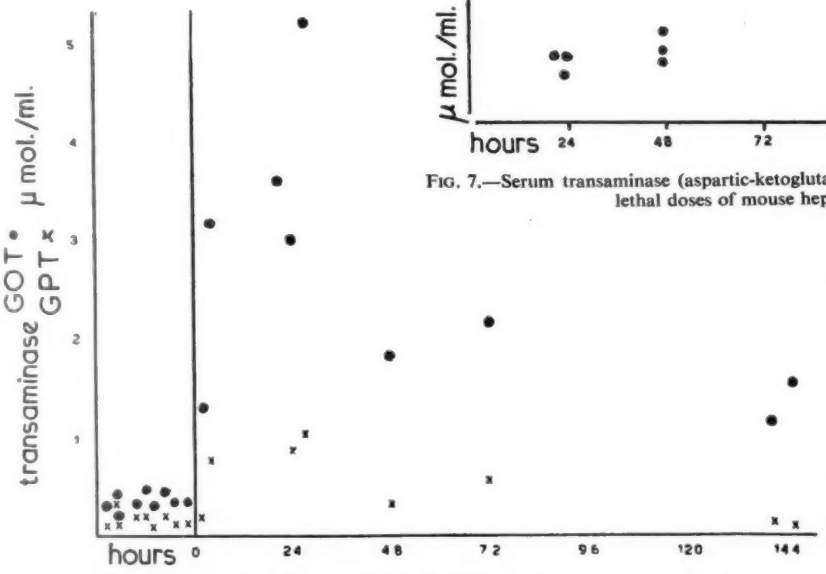


FIG. 6.—Serum transaminases in guinea pigs before and after ligature of the bile duct.

(2) In mice infected with mouse hepatitis by virus MHV_3 there was an increase of serum transaminases just as in human infectious hepatitis (Fig. 7), and this increase was preceded by a similar inversion of the ratio in the mitochondria of the damaged liver (Tolentino, Nordio and Rossi, 1957).

TABLE 1

VALUES OF LIVER TRANSAMINASES IN NORMAL AND IN TYPHOID-VACCINATED GUINEA-PIGS

Transaminase Activity	Normal			Vaccinated		
	GOT	GPT	Ratio GOT/GPT	GOT	GPT	Ratio GOT/GPT
Liver homogenate (μmol./100 mg.) ..	44·14	6·85	6.85	51·30	13·26	4.27
Mitochondria (μmol./mg. N) ..	9·78	1·14	8.48	9·00	3·66	2.90
Supernatant phase (μmol./mg. N.) ..	7·96	1·29	9.47	7·55	2·14	4.26

(3) In guinea-pigs immunized by typhoid vaccine an increase of alanine-ketoglutaric (GPT) transaminase in the mitochondria and in the supernatant fluid occurred with an alteration of the GOT/GPT ratio in favour of alanine-ketoglutaric (GPT) transaminase (Table 1) (Tolentino, 1957).

Previous research in our department had demonstrated that antigenic stimulation, such as provided by vaccination or infectious diseases, produces a hydropic swelling of the hepatic cells related to their increased function. The simultaneous internal displacement of transaminases in the cell may be responsible for the inversion of the serum transaminases (without a significant increase) in some infectious diseases. In infectious hepatitis the phases succeed each other: there is first, hydropic swelling with internal displacement of enzymes, followed by cellular necrosis and a consequent passage of cellular enzymes into the blood. In obstructive necrosis, produced by bile duct ligature, on the contrary, the first phase, the internal displacement of the enzymes, is absent and therefore there is no inversion of the ratio in the blood.

References

Kove, S., Goldstein, S. and Wróblewski, F. (1957). *Pediatrics*, 20, 590.

Ritis, F. de, Coltorti, M. and Giusti, G. (1955). *Minerva Med. (Torino)*, **46**, 1207.

Tolentino, P. (1957). Intern. Conference of Hepatol. Perugia.

——, Nordio, S. and Rossi, M. (1956). *Boll. Soc. ital. Biol. sper.*, **32**, 780.

—— and Rossi, M. (1957a). *Minerva pediat. (Torino)*, **9**, 377.

——, —— (1957b). *G. Mal. infett.*, **9**, 552.

Tonhazy, N. E., White, N. G. and Umbreit, W. W. (1950). *Arch. Biochem.*, **28**, 36.

Wróblewski, F. and La Due, J. S. (1954). *J Lab. clin. Med.*, **44**, 958.

A TEST FOR COELIAC DISEASE

BY

W. W. PAYNE and V. JENKINSON

From The Hospital for Sick Children, Great Ormond Street, London

(RECEIVED FOR PUBLICATION APRIL 28, 1958)

The relationship between wheat flour in the diet and the development of symptoms in children with coeliac disease observed by Dicke (1950) has been established. Subsequent investigations indicated that the injurious factor occurs principally in the gliadin fraction (van de Kamer, Weijers and Dicke, 1953). Weijers and van de Kamer (1955) used gliadin in a method of testing wheat sensitivity hoping that the test would be helpful in the diagnosis of coeliac disease.

In order to determine the value of this gliadin tolerance test, it was performed on a series of children with coeliac disease and on controls. The children with coeliac disease were patients of Dr. Wilfrid Sheldon and attended his clinic regularly. The diagnostic criteria used were those given by May (in Garrod, Batten and Thursfield, 1947). The diagnosis was confirmed by a favourable response to a diet free of wheat and rye gluten. The beneficial effect of the diet is manifested by an improvement in appetite and temperament, disappearance of steatorrhoea and an increase in growth. Growth is carefully followed by height and weight charts (Sheldon and Lawson, 1952).

Material

Thirty-three cases of coeliac disease were studied. The diagnosis was made according to the criteria stated in 25 cases. In eight cases the diagnosis was based on clinical data associated with the response to a gluten-free diet, and relevant biochemical investigations were not made.

The children were in all stages of the disease and treatment. Two of the children were in the active phase. Treatment had not been instituted when they were tested. Eight children had been on a gluten-free diet for periods of a few days to one month before their gliadin tolerance test. These children have since shown a satisfactory response to the therapeutic diet. The rest of the cases had been treated for some years, having had periods on a gluten-free diet and on a normal diet. Some children, who had been treated for more than four years, still deteriorated when returned to a normal diet. A few patients had apparently recovered after prolonged treatment; they had shown no recurrence of symptoms when returned to a normal diet and growth continued at the expected rate. Six children in this series were either undiagnosed or untreated for a long time after the onset of symptoms.

Control cases were selected from convalescent patients who had had diseases with no alimentary tract involvement, with the exception of one child, who was a normal healthy unlike twin of one of the coeliac patients. Four children who were convalescent from disorders of the alimentary tract from causes other than coeliac disease formed a second control group. A summary of the details of these cases is tabulated:

Case	Sex	Age (Yr.)	Diagnosis
A.H.	♀	2½	Dyschezia
N.H.	♂	7½	Malabsorption syndrome with abnormal pattern of second part of duodenum.
S.T.	♀	11	Chronic constipation with faecal incontinence. Congenital anal stenosis. Operation: division of fibrosed anal ring. Faecal incontinence continued. Vaginal septum.
M.K.	♀	11	Chronic watery diarrhoea. Giardia cysts found. Congenital atrial septal defect.

Gliadin was prepared according to the procedure recommended by van de Kamer (personal communication). The patient to be tested fasted, usually, for 12 hours; the period of fast was sometimes reduced to eight hours when the condition of the patient made it advisable, e.g. in the case of a young ailing child. A sample of blood was taken by fingerprick from a fasting subject into a heparinized tube. A dose of gliadin (350 mg./Kg. body weight) in water was fed to the patient, and hourly samples of blood were taken for five consecutive hours.

The plasma glutamine was estimated in each sample as glutamic acid (Prestcott and Waelsch, 1946, 1947). Free glutamic acid was removed by adsorption on acid alumina. The filtrate was hydrolyzed in acid medium

for one hour. The glutamic acid set free was separated on acid alumina and estimated. A glutamic acid standard was used in place of the solution recommended by Prestcott and Waelsch (1946). A series of standard curves were made and found to be linear over a range of 0-25 γ glutamic acid. A standard sample was estimated in parallel with test samples and all readings were related to it. The average difference between repeat estimations of 50 test samples drawn at random from our results was 0·7 mg./100 ml. Duplicate estimations were done when possible. It has been assumed that the glutamic acid liberated by short acid hydrolysis of the filtrate was entirely derived from the plasma glutamine; since other glutamine-containing compounds may contribute the measured substance is known as 'apparent' plasma glutamine (Prestcott and Waelsch, 1947).

Recording of Results

The maximum increase of apparent plasma glutamine occurred at variable times. The greatest increase, irrespective of time of occurrence, is recorded as a percentage of the fasting value, which is the form adopted by Weijers and van de Kamer (1955). There is no reason to suppose that there is any relation between the fasting plasma glutamine and the absolute increase after gliadin; therefore, the absolute increase in mg./100 ml. is also recorded. The results are given in the following tables.

Table 1 shows that the mean maximum increment of apparent plasma glutamine of these children with coeliac disease is significantly greater than that of normal children. A few children who had recently recovered from dysfunction of the alimentary tract show a mean percentage rise which is intermediate between that of normal children and coeliac children. The mean percentage in this group is not significantly different from children with no recent gastro-intestinal disturbance, nor from coeliac children. The absolute rise is the same as that of coeliac children.

Tables 2a and b show that there is no relation between age and magnitude of increase of apparent plasma glutamine in this series of controls and coeliac patients. The numbers of control children in different age groups are insufficient for a complete analysis, but there is no indication of an age relationship (Table 2a). Age can be disregarded when grouping the coeliac patients according to a clinical assessment (Table 2b).

Table 3 shows that the mean rise of apparent plasma glutamine of children treated for less than two years is significantly greater than that of normal children. Children who remained intolerant of gluten even after four years of treatment show a similar difference. There is no correlation in this series between magnitude of rise of apparent plasma glutamine and phase of the disease, whether symptoms are active or controlled by treatment.

The number of children who, after prolonged treatment, no longer appeared intolerant of gluten, was small. The mean rise of plasma glutamine did not differ significantly from normal children, but this may be the result of the limited size of the sample.

The six patients who remained undiagnosed or untreated for some time after the appearance of the disease were grouped together, but they do not form a homogeneous group. It is not surprising that their response to gliadin is variable.

TABLE 1

	No. of Estimations	Maximum Increment of Apparent Plasma Glutamine: As % of fasting value		mg./100 ml.	
		Mean	S.D.	Mean	S.D.
Controls:					
Group 1	13	22·62	21·53	1·04	1·10
Group 2 .. .. Children with recent alimentary dysfunction	5	40·80	17·55	2·42	1·21
Coeliac patients ..	38	51·24	37·32	2·42	1·38

Significance of difference between means of:

Control groups 1 and 2:	P>0·05	P>0·05
Control group 1 and coeliac group:	P<0·01	P<0·01
Control group 2 and coeliac group:	P>0·05	P>0·05

Using Cochran's approximation.

TABLE 2A

Control Children recovered from Diseases with no Alimentary Tract Involvement	No. of Estimations	Maximum Increment of Apparent Plasma Glutamine: As % of fasting value		mg./100 ml.	
		Mean	S.D.	Mean	S.D.
0-4 yr. ..	2	11		0·75	
5-9 yr. ..	6	30·67	20·62	1·42	1·06
10-14 yr. ..	5	12·4	22·01	0·70	1·18

TABLE 2B

Coeliac Patients	No. of Estimations	Maximum Increment of Apparent Plasma Glutamine: As % of fasting value		mg./100 ml.	
		Mean	S.D.	Mean	S.D.
0-4 yr. ..	13	54·23	40·91	2·24	1·39
5-9 yr. ..	19	55·37	38·76	2·71	1·46
10-14 yr.	6	31·67	18·34	1·88	1·01

Significance of difference between means of:

0-4 yr. and 5-9 yr.	P>0·05	P>0·05
0-4 yr. and 10-14 yr.	P>0·05	P>0·05
5-9 yr. and 10-14 yr.	P>0·05	P>0·05

Using Cochran's approximation.

TABLE 3

Independent Clinical Assessment of Children Tested	No. of Estimations	Maximum Increment of Apparent Plasma Glutamine As % of fasting value		mg./100 ml.	
		Mean	S.D.	Mean	S.D.
Controls:					
Group 1	13	22·62	21·53	1·04	1·10
Group 2 .. .. Children with alimentary dysfunction	5	40·80	17·55	2·42	1·81
Coeliac Patients:					
All cases treated less than 2 yr.	14	51·57	40·57	2·19	1·36
Intolerant of gluten after more than 4 yr. treatment	14	52·07	31·26	2·65	1·05
Recovered after long treatment	4	45·50	35·24	2·38	1·96
Treatment commenced late after onset of symptoms	6	52·33	52·14	2·48	1·92

Significance of difference between means of:

Control and coeliac patients:		
(*a*) Treated for less than 2 yr.	$P<0·05$	$P<0·05$
(*b*) Intolerant of gluten after more than 4 yr. treatment.	$P<0·05$	$P<0·01$
(*c*) Recovered after long treatment.	$P>0·05$	$P>0·05$
(*d*) Treatment commenced late after onset of symptoms.	$P>0·05$	$P>0·05$

Using Cochran's approximation.

Comparison of the mean rise of apparent plasma glutamine as a percentage of the fasting value of children who remained intolerant of gluten even after prolonged treatment and that of normal controls shows that the probability of the difference between the two results being due to chance, lies between 1 in 20 and 1 in 100. When the increase in mg./100 ml. is used instead, the probability is less than 1 in 100. The explanation of the difference lies in the fact that the fasting level of plasma glutamine tended to increase with age in these coeliac children. There are indications that the same trend may occur in normal children over a lower range, but in this case the trend was not significant. Further estimations are necessary to substantiate the indications of a rise of fasting level with age.

Table 4 shows that five children, who were tested while on a gluten-free diet and while on a normal diet, demonstrated no relationship between diet and rise of plasma glutamine.

In Table 5 the coeliac children were grouped according to the diet at the time of the test. The similarity of the mean rise in the two groups supports the conclusion that diet has no influence on the test.

None of the children with coeliac disease showed aggravation or recurrence of symptoms after the dose of gliadin used in the test.

Discussion

These results confirm the observations of Weijers and van de Kamer (1955), who found a greater increase of plasma glutamine in coeliac children than in normal children after ingestion of gliadin. The increase in our series of coeliac patients is not as great as that found by Weijers and van de Kamer. Alvey, Anderson and Freeman (1957), also found after a test dose of gluten an increase in blood glutamine which was greater in four coeliac children

TABLE 4

Effect of Diet on Increase of Apparent Plasma Glutamine

Patient	Age (yr.)	Gliadin Tolerance Test 1				Gliadin Tolerance Test 2			
		Diet	Period of Diet (mth.)	Maximum Increment of Plasma Glutamine %	mg./100 ml.	Diet	Period of Diet (mth.)	Maximum Increment of Plasma Glutamine %	mg./100 ml.
C.I. ..	14	G.F.D.	28	9	0·6	Normal	6	26	2·0
M. McC. ..	8	G.F.D.	30	45	1·7	Normal	4	41	3·6
C.M. ..	3	G.F.D.	15	77	4·3	Normal	5	13	1·2
L.P. ..	7	Normal	33	38	3·1	G.F.D.	8	79	4·2
J.A. ..	7	Normal	18	98	5·3	G.F.D.	4	23	1·1

G.F.D. = Gluten free diet.

TABLE 5

Diet	No. of Estimations on Coeliac Children	Maximum Increment of Apparent Plasma Glutamine As % of fasting value		mg./100 ml.	
		Mean	S.D.	Mean	S.D.
Gluten free	28	51·18	35·85	2·29	1·29
Normal	10	51·40	43·24	2·67	1·74

than in four normal children, but the increment was again of a lesser degree than that reported by Weijers and van de Kamer.

The intermediate position of children convalescent from gastro-intestinal disorders other than gluten-induced coeliac disease suggests that the abnormal increase of plasma glutamine may be a non-specific effect common to other gastro-intestinal disturbances. The number of these children tested was too small to show conclusive evidence.

The increase of plasma glutamine measured in five children tested while on a gluten-free diet and on a normal gluten-containing diet showed no correlation with the prevailing diet. The results from these children exhibit considerable variation between two tests in the same child. A very wide standard deviation is evident in this series indicating an overlap in the range of results from the various groups. The variance found in the results from the coeliac group is significantly greater than that in the control group of children with no recent gastro-intestinal dysfunction (Table 1). This probably reflects the unreliability of a test dependent on rate of absorption in children where absorption is disturbed (Alvey, *et al.*, 1957). We would conclude in accordance with other workers that the test in its present form is unreliable in individual cases.

Later experiments by van de Kamer and Weijers (1955) showed that it was glutamine bound in protein, as it occurs in gliadin, which probably caused the abnormal increase of apparent plasma glutamine in children with coeliac disease and was the injurious factor. Frazer (1956) reported the presence of abnormally large amounts of a glutamine-containing peptide in the blood of one patient fed with a peptide fraction obtained from a tryptic digest of wheat gluten. The toxicity of this fraction was eliminated after digestion by an extract of pig's intestinal mucosa. The work of Alvey *et al.* (1957) substantiates the evidence indicating that the toxic factor in gluten is probably a peptide. They were able to show that the smaller peptides of gluten caused an increase of fat excretion in a patient with mild clinical symptoms.

The difference between normal children and children with coeliac disease is sufficiently pronounced to encourage further investigation of the amino-acid and peptide pattern of the blood after ingestion of gliadin or fractions of this protein.

Summary

A gliadin tolerance test was performed on control children and children with coeliac disease.

The increase of apparent plasma glutamine after a test dose of gliadin is significantly greater in children with coeliac disease than in control children convalescent from diseases with no gastro-intestinal involvement. A small group of children convalescent from gastro-intestinal dysfunction from causes other than coeliac diseases showed an increase intermediate between normal controls and coeliac children.

There is no quantitative relation between increase of plasma glutamine and phase of the disease, whether acute or non-symptomatic through withdrawal of wheat and rye gluten from the diet.

Diet appears to have no influence on the degree of increase of plasma glutamine.

The overlap of range of results from controls and coeliac patients is considerable and does not recommend the test as a diagnostic one.

We wish to thank Dr. Wilfrid Sheldon and other members of the staff for allowing us access to their patients. We are grateful to Dr. Sheldon for his help and interest in the study and to Dr. C. O. Carter for his tuition and advice on methods of statistical analysis. We are also indebted to Mr. A. Whitfield for his skilled assistance in the laboratory.

This investigation was done under the auspices of the Research Committee, The Hospital for Sick Children, Great Ormond Street.

References

Alvey, C., Anderson, C. M. and Freeman, M. (1957). *Arch. Dis. Childh.*, **32**, 434.
Dicke, W. K. (1950). *Coeliakie*. M.D. Thesis. Utrecht.
Frazer, A. C. (1956). *Proc. roy. Soc. Med.*, **49**, 1009.
Garrod, A. E., Batten, F. E. and Thursfield, H. (1947). *Diseases of Children*. 4th ed. Edited by Paterson, D. and Moncrieff, A. A., **1**, 343. London.
Kamer, J. H. van de. Personal communication.
—— and Weijers, H. A. (1955). *Acta paediat.* (*Uppsala*), **44**, 465.
——, —— and Dicke, W. K. (1953). *Ibid.*, **42**, 223.
Prestcott, B. A. and Waelsch, H. (1946). *J. biol. Chem.*, **164**, 331.
——, —— (1947). *Ibid.*, **167**, 855.
Sheldon, W. and Lawson, D. (1952). *Lancet*, **2**, 902.
Weijers, H. A. and Kamer, J. H. van de (1955). *Acta paediat.* (*Uppsala*), **44**, 536.

A LONGITUDINAL STUDY OF THE GROWTH AND DEVELOPMENT OF PREMATURELY AND MATURELY BORN CHILDREN

PART I. INTRODUCTION

BY

CECIL MARY DRILLIEN

From the Department of Child Life and Health, Edinburgh

(RECEIVED FOR PUBLICATION DECEMBER 16, 1957

Over the past 40 years many studies of the later growth and development of premature infants have been reported in the literature with widely varying conclusions (for example: Ylppö, 1920; Capper, 1928; Hess, Mohr and Bartelme, 1934; Blegen, 1952; Alm, 1953). In a comprehensive review of the early literature Benton (1940) puts forward four reasons for its contradictory nature. These are: the substitution of 'clinical impression' for standardized tests; the lack of attention paid to socio-economic factors; inadequate numbers and unsatisfactory controls; and the biased nature of the samples.

The longitudinal developmental study which is described in this paper has been designed to take into account these important points.

The chief difficulty in planning a long-term study of this type is to obtain the co-operation of parents representing a cross section of the general population, and having gained co-operation to maintain it over a period of years. This is well illustrated by reference to some current long-term studies. For the longitudinal research in child development being carried out from the Child Study Centre, London (Moore, Hindley and Falkner, 1954), the parents of 18·4% of the 272 children originally selected, declined to participate in the study at the beginning. In a similar study from the Centre International de l'Enfance, Paris, 16% of the 515 children were never seen. In addition it was reported (Pernot, 1955) that not more than 15% attended all seven of the examinations arranged during the first two years.

Present Study

During the period 1953 to 1955, over 1,000 mothers delivered in two large Edinburgh maternity hospitals took part in an investigation into the social factors affecting premature birth (Drillien, 1957). Every surviving premature infant and every pair of twins was selected for the developmental study, the only stipulation being that the family be resident in Edinburgh and likely to be so for the next six months. Illegitimate infants were only excluded if adoption was proposed. The sample so obtained was heavily weighted by the larger premature babies between 4½ and 5½ lb. at birth. It was therefore decided to include all babies of 4 lb. or less, who were resident in the surrounding counties.

The control group of infants who were mature at birth, on a weight basis, was selected by taking the next mature birth from the hospital record list occurring after every alternate premature birth. This method of obtaining a control sample has been chosen in preference to the commonly used matching technique (e.g., Douglas and Mogford, 1953) which is based on the assumption that social and economic differences between two groups will be removed by matching for certain broad categories such as social class, sex, age of parents, place in family and locality. This method has not been employed in the present study as it was felt that many more diverse influences affect the later growth and development of the child than can be covered by taking into account a few broad groupings. It has, in fact, been noticed on many occasions that two neighbouring families matched closely by such factors may show widely differing standards of child care and household management.

The mothers were not asked initially to co-operate in a long-term survey, but were asked to allow a visit and examination when their baby was 6 months old. At this time every mother agreed to co-operate, although later two withdrew their consent. Table 1

gives the total numbers of children originally recruited, by sex and birth weight. Tables 2 and 3 give the numbers of twin pairs and the birth weight distribution of individual twins by sex. It was hoped that after the first visit at 6 months of age, the mothers would be sufficiently interested to continue co-operation and this has, in fact, been the case. Losses from the sample have been minimal and have been due mainly to emigration, or removal to a considerable distance (i.e., more than 30 or 40 miles). Children who were grossly mentally defective were removed from the sample after one year if the diagnosis had been established. Two children were lost from the sample in the first two years for this reason. Table 4 gives the number of examinations completed at 6, 12, 18 and 24 months of age, the number of examinations missed and losses from the sample. Out of the original 595 children recruited, 544 (91·4%) remained in the survey at 2 years.

Although at the time these children were born about 75% of all Edinburgh births took place in hospital, it seemed possible that a sample of children selected from hospital deliveries only might be biased, particularly as regards social background and parity of the mother. All births in Edinburgh are notified to the Public Health Department of the Corporation as being under or over 5½ lb. at birth, and access to these records was allowed. It was therefore decided to obtain some comparative information about all births in Edinburgh during the 12-month period October, 1953, to October, 1954 (Drillien and Richmond, 1956). Every premature birth together with one in 10 of all mature births was investigated and the following information recorded about each: birth weight, legitimacy, age of mother, parity and occupation of the father.

The survey sample can therefore be compared with the general infant population to see how far the two are alike and in drawing any general conclusions from the sample cognisance can be taken of the differences observed.

Tables 5 and 6 give the parity and social class distribution of the survey sample as compared with the general population, for premature infants of

TABLE 1

TOTAL NUMBER OF SINGLETONS ORIGINALLY RECRUITED BY BIRTH WEIGHT AND SEX

Birth Weight (lb. oz.)	M.	F.	Total
3·0 and under	10	4	14
3·1–3·8	13	15	28
3·9–4·0	14	12	26
4·1–4·8	18	20	38
4·9–5·0	30	25	55
5·1–5·8	37	53	90
5·9–6·8	6	14	20
6·9–7·8	22	27	49
7·9–8·8	21	14	35
8·9 and over	9	6	15
Total	180	190	370

TABLE 2

TOTAL TWIN PAIRS ORIGINALLY RECRUITED

Twin Pairs of Unlike Sex:		
Both over 5½ lb.	14	
Both under 5½ lb.	22	
Male over 5½ lb., female under 5½ lb.	7	
Female over 5½ lb., male under 5½ lb.	6	
Total	49	
Twin Pairs of Like Sex, Identical:	F.	M.
Both over 5½ lb.	1	2
Both under 5½ lb.	11	7
One over 5½ lb., one under 5½ lb.	1	5
Total	13	14
Twin Pairs of Like Sex, not Identical:	F.	M.
Both over 5½ lb.	7	7
Both under 5½ lb.	3	5
One over 5½ lb., one under 5½ lb.	7	5
Total	17	17
Surviving Twin of Like Sex, Other Twin Stillborn or Died Before Discharge	F.	M.
Over 5½ lb.	1	1
Under 5½ lb.	2	1
Total	3	2
Total no. of twin pairs	110	
Total no. of twin pairs one only surviving	5	
Total no. of infants	225	

TABLE 3

BIRTH WEIGHT DISTRIBUTION OF TWINS RECORDED SEPARATELY BY SEX

Birth Weight (lb. oz.)	M.	F.	Total
3·0 and under	2	6	8
3·1–3·8	1	3	4
3·9–4·0	12	7	19
4·1–4·8	15	13	28
4·9–5·0	11	17	28
5·1–5·8	22	21	43
5·9–6·8	30	22	52
6·9–7·8	15	18	33
7·9–8·8	5	5	10
Total	113	112	225

TABLE 4

LOSSES FROM SAMPLE

Age (months)	Total	Examination Completed	Examination not Completed	Lost from Sample*
6	595	572	13	10
12	585	564	3	18
18	567	548	5	14
24	553	538	6	9

*Total 51: death (9); refused to co-operate (7); moved or emigrated (33); removed from sample because of gross mental defect (2).

TABLE 5

PARITY DISTRIBUTION, EXPRESSED AS PERCENTAGE, OF SURVEY SAMPLE COMPARED WITH ALL INFANTS BORN IN EDINBURGH, 1953 TO 1954

Birth Weight (lb. oz.)	Parity											
	0		1		2		3		4		5 and over	
	Survey	Edin.	Survey	Edin.	Survey	Edin.	Survey	Edin.	Survey	Edin.	Survey	Edin.
>5·8	58·9	36·6	21·0	27·9	15·1	15·5	3·4	8·0	0·8	8·0	0·8	6·0
4·1 to 5·8	56·8	48·9	20·8	22·6	10·4	14·7	6·6	5·1	6·6	5·1	2·7	4·6
<4·1	47·1	51·0	19·1	14·9	19·2	12·8	11·8	12·8	11·8	12·8	—	8·5

TABLE 6

SOCIAL CLASS DISTRIBUTION, EXPRESSED AS PERCENTAGE, OF SURVEY SAMPLE COMPARED WITH ALL INFANTS BORN IN EDINBURGH, 1953 TO 1954

Birth Weight (lb. oz.)	Social Class					
	1 and 2		3		4 and 5	
	Survey	Edin.	Survey	Edin.	Survey	Edin.
>5·8	21·8	26·9	55·5	53·6	22·7	19·5
4·1 to 5·8	15·3	12·5	51·4	57·1	33·3	30·4
<4·1	14·7	19·1	66·2	55·4	19·1	25·5

4 lb. or less at birth, those between 4 lb. 1 oz. and 5 lb. 8 oz., and those mature at birth.

The social class distribution of the survey sample and the Edinburgh infants is very close and appropriate statistical tests show that there is no reason to suppose that the survey sample is biased in any way with respect to social class distribution.

Parity distribution in the premature groups is also sufficiently close to be free from bias, but in the mature control group there is an excess of first births in the survey sample, which must be taken into account in drawing general conclusions about the effect on the child of place in family.

As nearly all twin pregnancies are delivered in hospital, it has been assumed that the sample of twins will be representative of twins in the general population.

Procedure and Methods

Hospital Interview. All mothers were interviewed in the maternity hospital and consent to the initial visit obtained. At the same time particulars were noted of the mother's social background both before marriage and since, and any complication of the pregnancy or delivery.

First Home Visit at Six Months. At the initial home visit a special effort was made to establish a good relationship with the mother and to secure her continuing interest in the survey.

Full particulars were taken of housing and certain information was obtained about other children in the family. Details of feeding, vitamin supplements, and protective immunization were noted. At this and every subsequent interview a record was made of any illness necessitating medical attention or hospital admission.

A brief clinical examination was carried out and the children graded as to general nutrition and health, and a note made of any minor abnormalities which had not received medical attention. The children were weighed in light, indoor clothing, an appropriate deduction being made for the clothes worn, and, from the age of 2 years, crown-heel and crown-rump lengths were taken recumbent on a portable measuring board.

The developmental level was estimated on the response to the Gesell developmental tests.

Subsequent Examinations. The children are seen every six months (± 7 days) up to the age of 18 months and at 2 years old (± 14 days) and thereafter they are seen once yearly (± 14 days). It was originally anticipated that after the initial visit a proportion of the mothers would be willing to bring their babies for examination to a central clinic, thus saving much time and providing standard conditions for examination and testing. In practice it has been found that the number of mothers who are willing to do this is very small. Even the best-intentioned find it difficult to attend regularly at a set time especially if there are other children in the family. Mothers from the two extremes of the social scale are the most reluctant to attend a clinic, and insistence on such attendance inevitably introduces bias in the social composition of the sample. In many cases the mother has become pregnant again during the course of the survey, and this is an added deterrent to further clinic attendance.

Mental testing may be difficult, especially after the first year, in the presence of other members of the family and absence of adequate table and floor space. Nevertheless as the children are seen at regular

intervals an incomplete testing at one visit can be confirmed and completed on the next occasion.

Some authorities hold strongly to the view that developmental testing can not be considered valid unless carried out under standard conditions. This would be more convincing if the subjects for testing came from a standard environment. It may be argued that the child's own house approximates more nearly to a standard setting than an impersonal clinic room to which children from different types of homes react in a different way. In practice it has been found that the children who have been tested both at home and in the clinic are more responsive in their own homes.

Table 7 gives the proportion of children seen within the pre-arranged period. Up to 18 months quite a large percentage were examined more than seven days after the set age. In some cases, this was due to illness of mother or child, or absence on holiday, but in the majority it was due to a change of address and the inevitable lapse of time before the family could be traced and a fresh appointment made. One hundred and ninety-five changes of address have been recorded. This is 35% of total families and does not include those who have been lost to the survey by removal. Nearly all were seen within 14 days, and it will be noticed that at 2 years old (± 14 days) only a small percentage were not seen within this period. A suitable adjustment has been made for measurements and estimated developmental levels if the child was seen within four weeks of the pre-arranged date. Measurements for children seen later than four weeks have not been included in the subsequent analyses.

Although much of the information collected is necessarily subjective in character, an attempt has been made to adhere to certain standards throughout. Some of these are now described.

TABLE 7

PERCENTAGE OF CHILDREN SEEN LATER THAN PRE-ARRANGED DATE

Age (mths.)	%
6 ± 7 days	14
12 7 days	10
18 7 days	11
24 ±14 days	5

Housing

The following criteria were employed in grading housing accommodation:

(1) A separate living room not used for sleeping. (2) Sufficient bedrooms for the child in question to sleep apart from the parents after the age of 1 year and with not more than two other children of the same sex, or one adult. (3) Adequate furnishings, in particular that the child should be able to occupy a separate cot or bed. (4) Modern cooking facilities (gas or electric cooker), and a kitchen sink. (5) A supply of hot water. (6) A bathroom. (7) An inside W.C. (8) Easy access to a garden or green. (9) A reasonable standard of cleanliness and structural repair.

The following classification was adopted according to the number of points satisfied:

1=Very good	9
2=Good	7 to 8
3=Fairly good	5 to 6
4=Fair	3 to 4
5=Poor	1 to 2
6=Very poor	0

The majority of municipally owned houses were classified as very good, although some come in the next category as they failed to satisfy points 3 and 9. The majority of privately owned houses belonging to parents in social classes 1 and 2, also were graded as being very good. Privately owned houses belonging to families in social class 3, were usually graded as good, or fairly good, overcrowding being the commonest problem here.

Many rented houses occupied by families in social classes 3, 4 and 5 were graded as fair or poor, these most often being of the room and kitchen type, without a bathroom or hot water, and often with a shared toilet on the landing.

Houses graded as very poor possessed none of the facilities mentioned above and in addition were kept in a state of squalor and filth.

A house which might have been considered good or fairly good when the child was under 1 year old, and the only child in the family, might drop to a lower category at a later age and when other children were born.

Fig. 1 gives the percentage of singletons in the survey living in these grades of accommodation at 6 months by social class.

As would be expected there is a marked social gradient in the standard of accommodation. In social classes 1 and 2, 91% were occupying houses graded as good or very good, compared with 27% in social classes 4 and 5. Of the total population studied 54% were living in good or very good accommodaton and 27% in poor or very poor houses. By the age of 2 years the situation had improved a little, 58% now living in good accommodation and 20% in poor. In 16% of the total, the housing had improved due mainly to rehousing by the municipal authority and in 4% the housing had deteriorated.

Social Class

The social class of the child's father has been

recorded, the classification used being based on that given by the Registrar General (1951) in the Classification of Occupations, 1950, with certain minor modifications (Drillien, 1957) principally the addition of a social class 6 to cover homes in which the mother was widowed, divorced or separated from her husband, or where the child was illegitimate.

In addition to the social class classification, working class mothers and fathers, if seen, have been graded as being superior working class, average or poor.

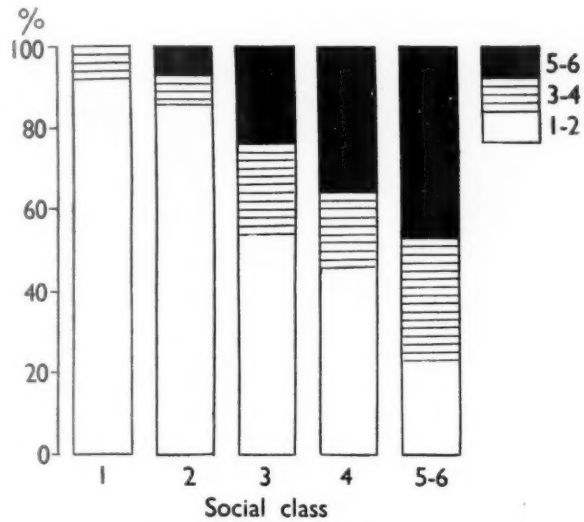


FIG. 1.—Standard of housing by social class.

Maternal Efficiency

The following points were noted when considering the efficiency of the mother: (1) Cleanliness of the house, the child and his clothes. (2) Feeding habits and diet. (3) Advantage taken of welfare facilities, such as vitamin supplements, protective immunization and infant clinics. (4) Management of training problems such as weaning, sleeping and toilet training. (5) The relationship of the mother with the child, other children in the family, and the father. (6) Maternal health.

Maternal efficiency was graded as being: very good, good, fair and poor. This grading was necessarily a purely subjective assessment, but is considered valid as all examinations were carried out by the same person and the same standards adopted throughout. In some cases the grading of efficiency changed as the child grew older. The mother who could deal adequately with a baby might prove less capable of coping with a toddler. The standards of others though satisfactory with the first child became less satisfactory as succeeding pregnancies entailed more work and responsibility.

Some mothers, especially those in the higher social groups, with an only child, though giving every material care and much affection, yet were over-anxious and fussy in their handling. A separate note has been made of this and it appears to have some bearing on the genesis of behaviour problems, which will be dealt with in a separate paper.

Fig. 2 gives the grading of maternal efficiency by social class at the initial home visit. In the total sample, maternal care was graded as good, or very good, in 84% of homes. This comes very close to the findings in the Newcastle 1,000-family survey (Spence, Walton, Miller and Court, 1954) in which at least 85% of the families were regarded as receiving a good standard of child care.

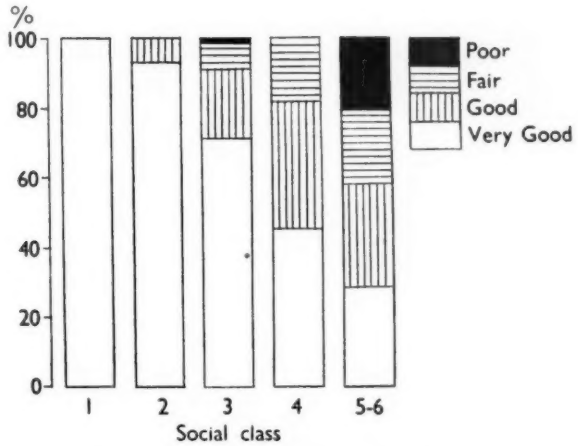


FIG. 2.—Efficiency of the mother by social class.

Again there is a marked social gradient. In social classes 1 and 2, maternal efficiency was considered good or very good in 100% of cases, compared with less than 60% in social class 5. In one-fifth of homes in this latter group, maternal efficiency was considered poor. The children were found to be dirty, inadequately clothed and fed, subject to a disproportionate amount of illness, and in many cases lacking in security and affection.

At 2 years of age the percentage of maternal efficiency graded as fair or poor had risen from 16% to 20%, mainly due to deterioration in standards with succeeding pregnancies in social class 5.

All children in the survey have now reached the age of 2 years and subsequent papers will present the data collected for this age period under the following headings: (1) Physical growth in relation to birth weight, height of parents, nutrition, early

illness and social class. (2) Mental development in relation to birth weight, gestation time and social class. (3) Morbidity in relation to nutrition, maternal efficiency, place in family, housing and social class. (4) Patterns of maternal care.

References

Alm, I. (1953). *Acta paediat.* (*Uppsala*), **42**, Suppl. 94.
Benton, A. L. (1940). *Amer. J. Orthopsychiat.*, **10**, 719.
Blegen, S. D. (1952). *Acta paediat.* (*Uppsala*), **41**, Suppl. 88.
Capper, A. (1928). *Amer. J. Dis. Child.*, **35**, 262.
Douglas, J. W. B. and Mogford, C. (1953). *Brit. med. J.*, **1**, 748.
Drillien, C. M. and Richmond, F. (1956). *Arch. Dis. Childh.*, **31**, 390.
—— (1957). *J. Obstet. Gynaec. Brit. Emp.*, **64**, 161.
Hess, J. H., Mohr, G. J. and Bartelme, P. F. (1934). *The Physical and Mental Growth of Prematurely Born Children.* Chicago.
Moore, T., Hindley, C. B. and Falkner, F. (1954). *Brit. med. J.*, **2**, 1132.
Pernot, M. P. (1955). *Études sur la Croissance Somatique et le Développement Psychique de l'Enfant.* Paris.
Registrar General (1951). Classification of Occupations, 1950. London.
Spence, J., Walton, W. S., Miller, F. J. W. and Court, S. D. M. (1954). *A Thousand Families in Newcastle Upon Tyne.* London.
Ylppö, A. (1920). *Z. Kinderheilk.*, **24**, 1

A LONGITUDINAL STUDY OF THE GROWTH AND DEVELOPMENT OF PREMATURELY AND MATURELY BORN CHILDREN

PART II.—PHYSICAL DEVELOPMENT

BY

CECIL MARY DRILLIEN

From the Department of Child Life and Health, Edinburgh

(RECEIVED FOR PUBLICATION DECEMBER 16, 1957)

This paper is the second in a series presenting findings in a long-term study of growth and development in a representative sample of nearly 600 premature and maturely born children, delivered in two Edinburgh maternity hospitals in the years 1953 to 1955. The sample, the method of selection, the procedures carried out and the social standards employed have already been described in Part I (Drillien, 1958).

All children in the survey have reached the age of 2 years, and results are now given of the analysis of weight and height measurements, in the first 2 years of life for different birth weight groups in relation to certain genetic and environmental factors. The children were examined at 6, 12, 18 and 24 months of age. At 6 months, infants were weighed on baby scales recording accurately to 1 oz. Thereafter they were weighed on a spring balance type of scale incorporating a seat. These scales are calibrated in ounces up to a weight of 50 lb., but are only considered to be accurate to the nearest 4 oz. Both scales were checked periodically against standard weights. The children were weighed in light indoor clothes, without shoes, and an appropriate deduction made for the clothes still worn. At 2 years old recumbent length without shoes was recorded on a portable measuring board calibrated in centimetres.

Mean Measurements of Weight and Height

Tables 1 to 4 give mean weights, weight increments and standard deviation of these means, at ages 6, 12, 18 and 24 months, for four birth weight groups, of male and female singletons and twins. At each age, mean weight is related to birth weight, the prematurely born showing little tendency to reduce their initial weight handicap. At 2 years the total weight increment since birth for singletons is highest in the smallest birth weight group. The difference between means of the group 4½ lb. or less at birth, and that over 7½ lb. at birth is 14 oz. for males and 13 oz. for females. The appropriate statistical test shows that a difference of this magnitude is not significant at the 5% point.

In the case of multiple births, the differences in mean weight at 2 years are greater than the differences in mean birth weight, both male and female twins showing smaller weight increments in the lower birth weight groups. Again these differences are not statistically significant.

Table 5 gives mean heights and height increments at 2 years for the same birth weight groups. Here again those who were largest at birth maintain their superiority in height at 2 years, but the height increments for both male and female singletons and twins are greater for those smallest at birth. Here the difference in height increment is statistically significant. There appears to be a definite tendency for those smallest at birth to reduce their height handicap significantly by 2 years of age.

Among singletons, boys show a bigger weight increment than girls at 2 years, amounting to just over 1 lb. both for those premature and mature at birth. In the twin groups the boys again show a bigger weight increment of ½ lb. for those 5½ lb. or less at birth, and 1½ lb. for those above that birth weight. There is very little difference between the sexes in height increment either for single or multiple births.

These results are similar to those given by Lowe and Gibson (1953) who found that mean weight was closely related to birth weight, but that there was

TABLE 1

MALE SINGLETONS. MEAN WEIGHTS AND WEIGHT INCREMENTS FOR DIFFERENT BIRTH WEIGHT GROUPS

Age (mth.)	Birth Weight (lb. oz.)	Weight (oz.)	S.D.	Weight Increment (oz.)	S.D.	No.
6	4·8 and under	219	4·1	159	3·7	46
	4·9 to 5·8	250	4·1	169	3·9	60
	5·9 to 7·8	281	6·8	171	6·8	28
	7·9 and over	297	4·5	160	3·9	30
12	4·8 and under	308	6·4	251	6·1	53
	4·9 to 5·8	336	4·5	254	4·5	62
	5·9 to 7·8	366	8·3	255	8·6	26
	7·9 and over	383	6·7	246	6·6	30
18	4·8 and under	353	6·5	297	6·0	51
	4·9 to 5·8	374	4·4	292	4·3	64
	5·9 to 7·8	413	9·3	302	9·6	26
	7·9 and over	428	8·4	291	8·0	29
24	4·8 and under	394	6·6	335	6·5	53
	4·9 to 5·8	408	4·8	327	5·1	62
	5·9 to 7·8	439	8·5	328	8·3	26
	7·9 and over	457	8·9	321	8·7	30

TABLE 2

FEMALE SINGLETONS. MEAN WEIGHTS AND WEIGHT INCREMENTS FOR DIFFERENT BIRTH WEIGHT GROUPS

Age (mth.)	Birth Weight (lb. oz.)	Weight (oz.)	S.D.	Weight Increment (oz.)	S.D.	No.
6	4·8 and under	216	7·3	155	4·1	47
	4·9 to 5·8	227	3·9	152	6·9	75
	5·9 to 7·8	260	8·7	152	3·8	40
	7·9 and over	271	6·1	139	6·5	20
12	4·8 and under	307	6·7	248	3·6	41
	4·9 to 5·8	320	6·5	243	4·8	77
	5·9 to 7·8	339	6·5	231	6·1	39
	7·9 and over	367	9·9	239	11·5	20
18	4·8 and under	352	6·3	294	6·0	43
	4·9 to 5·8	359	5·1	277	5·0	75
	5·9 to 7·8	380	6·2	266	5·3	37
	7·9 and over	407	9·7	271	8·4	19
24	4·8 and under	390	6·8	324	11·0	42
	4·9 to 5·8	395	5·9	314	5·5	75
	5·9 to 7·8	414	5·5	306	6·4	38
	7·9 and over	440	10·4	309	9·9	19

TABLE 3

MALE TWINS. MEAN WEIGHTS AND WEIGHT INCREMENTS FOR DIFFERENT BIRTH WEIGHT GROUPS

Age (mth.)	Birth Weight (lb. oz.)	Weight (oz.)	S.D.	Weight Increment (oz.)	S.D.	No.
6	4·8 and under	222	6·5	158	5·8	28
	4·9 to 5·8	241	5·3	158	5·3	31
	5·9 to 7·8	272	4·6	171	4·8	42
	7·9 and over	298	4·8	174	6·2	5
12	4·8 and under	296	7·2	235	7·9	25
	4·9 to 5·8	327	9·0	248	9·6	28
	5·9 to 7·8	362	5·8	257	5·7	39
	7·9 and over	365	8·9	240	9·4	6
18	4·8 and under	353	7·6	285	7·8	27
	4·9 to 5·8	378	7·5	294	7·3	29
	5·9 to 7·8	402	6·9	300	6·8	37
	7·9 and over	409	12·2	285	13·0	6
24	4·8 and under	376	8·4	312	8·5	27
	4·9 to 5·8	410	7·1	327	7·2	28
	5·9 to 7·8	442	7·4	343	7·8	39
	7·9 and over	450	17·8	325	18·8	5

TABLE 4

FEMALE TWINS. MEAN WEIGHTS AND WEIGHT INCREMENTS FOR DIFFERENT BIRTH WEIGHT GROUPS

Age (mth.)	Birth Weight (lb. oz.)	Weight (oz.)	S.D.	Weight Increment (oz.)	S.D.	No.
6	4·8 and under	204	5·8	144	4·6	30
	4·9 to 5·8	239	5·1	157	5·1	34
	5·9 to 7·8	263	6·6	158	6·4	34
	7·9 and over	283	12·8	152	10·5	4
12	4·8 and under	290	7·5	230	7·4	30
	4·9 to 5·8	320	12·9	242	7·6	32
	5·9 to 7·8	342	6·4	241	6·5	36
	7·9 and over	379	11·2	250	9·2	5
18	4·8 and under	338	9·8	277	9·0	29
	4·9 to 5·8	367	7·5	288	7·4	32
	5·9 to 7·8	387	6·4	284	6·0	34
	7·9 and over	427	18·7	322	29·0	4
24	4·8 and under	373	8·0	310	7·7	30
	4·9 to 5·8	390	10·1	310	10·1	28
	5·9 to 7·8	415	5·9	313	5·7	33
	7·9 and over	466	6·6	340	5·7	5

TABLE 5

MEAN HEIGHTS AND HEIGHT INCREMENTS AT TWO YEARS FOR DIFFERENT BIRTH WEIGHT GROUPS

	Birth Weight (lb. oz.)	Height (cm.)	S.D.	Height Increment (cm.)	S.D.	No.
Male Singletons	4·8 and under	81·1	1·7	38·9	·9	52
	4·9 to 5·8	84·0	·37	37·9	·47	63
	5·9 to 7·8	86·8	1·47	36·5	·91	26
	7·9 and over	87·4	·58	35·4	·63	29
Male Twins	4·8 and under	82·3	·85	38·6	·71	24
	4·9 to 5·8	83·8	·61	37·0	·77	28
	5·9 to 7·8	86·3	·53	36·9	·63	38
	7·9 and over	84·8	·80	33·4	1·07	5
Female Singletons	4·8 and under	82·7	·65	39·5	·64	42
	4·9 to 5·8	83·2	·43	36·8	·45	74
	5·9 to 7·8	85·2	·53	38·0	·72	37
	7·9 and over	86·4	·68	34·9	·66	19
Female Twins	4·8 and under	80·7	·65	38·1	·67	28
	4·9 to 5·8	82·3	·71	36·3	·79	28
	5·9 to 7·8	84·4	·63	34·9	·77	32
	7·9 and over	87·5	·37	36·9	·94	5

little correlation between weight increment and birth weight. At 3 years the average male increment was 1 lb. greater than that for females. Similarly Falkner (1958) found that the mean weight increment from birth to 2 years was 1½ lb. greater for boys, but there was no difference in mean recumbent length increment for boys and girls between 4 weeks and 2 years of age. He also states that birth weight and early length differences are maintained up to the age of 3 years.

The Effect on Height and Weight of Certain Environmental Factors

It is known that prematurely born children tend to come from an inferior socio-economic background, which may account in part for their failure to catch up in weight and height with those mature

at birth. Information was collected about the environmental background of each case, including the standard of maternal efficiency, frequency of illness and adequacy of the diet.

Maternal efficiency has been graded as: (1) Very good, (2) Good, (3) Fair and (4) Poor. Diet has been graded as: (1) Good, (2) Fair and (3) Poor. Frequency of illness has been graded according to the number of medical conditions requiring attention from the family doctor or hospital admission as follows: (1) No illness. (2) A few minor disorders, e.g., head colds, mild digestive disturbances or mild attacks of specific fevers. (3) One to three more serious infections, e.g., bronchitis, tonsillitis, otitis media or one hospital admission. (4) Four or more infections as above and one hospital admission. (5) Four or more infections and two hospital admissions. (6) Four or more infections and three or four hospital admissions. (7) Four or more infections and five or more hospital admissions. Hospital admissions for surgical conditions such as hernia or pyloric stenosis have not been included.

Table 6 gives mean weight and height increments at 2 years, for three birth weight groups, by four grades of maternal efficiency. Weight and height increments are substantially higher when maternal efficiency is very good, the effect of maternal efficiency being most marked in those who were premature at birth. Table 7 gives similar means by frequency of medical illness, here graded as: A, no serious illness (1 and 2), B, some illness (3), and C, frequent illness (4, 5, 6 and 7). Again the prematurely born with little or no illness show a marked increase in weight and height increments especially in those smallest at birth. Analyses of weight and height increment by grade of diet are given in Table 8 and show a similar result. Tables 9, 10 and 11 give the proportion of children in the three birth weight groups, by the different efficiency, illness and diet grades.

In the premature groups there is a striking excess of inefficient mothers, frequent illness and poor diet, especially in those who were 4½ lb. or less at birth. To get some idea of the extent to which prematurely born children might catch up in weight and height if they were reared in the most favourable environ-

TABLE 6
MEAN WEIGHT AND HEIGHT INCREMENTS AT TWO YEARS BY EFFICIENCY GRADE OF MOTHER

	Male			Female		
Birthweight (lb. oz.)	4·8 and under	4·9 to 5·8	5·9 and over	4·8 and under	4·9 to 5·8	5·9 and over
			Weight Increment (oz.)			
Efficiency						
1	347·4	339·0	326·2	328·2	342·2	316·4
2	316·7	311·4	345·1	312·3	311·5	300·0
3	329·3	326·4	346·4	306·1	300·1	304·8
4	295·0	320·7	321·5	281·7	266·8	287·6
Difference between 1 and 4	52·4	18·3	4·7	46·5	75·4	28·8
			Height Increment (cm.)			
Efficiency						
1	39·1	39·3	36·4	39·9	37·2	36·1
2	39·1	36·9	36·4	38·1	36·5	35·4
3	39·3	35·8	36·0	38·8	36·8	33·4
4	33·8	34·6	33·0	36·1	31·7	34·1
Difference between 1 and 4	5·3	4·7	3·4	3·8	5·5	2·0

TABLE 7
MEAN WEIGHT AND HEIGHT INCREMENTS AT TWO YEARS BY FREQUENCY OF ILLNESS

	Male			Female		
Birthweight (lb. oz.)	4·8 and under	4·9 to 5·8	5·9 and over	4·8 and under	4·9 to 5·8	5·9 and over
			Weight Increment (oz.)			
Illness						
A	352·7	334·9	333·5	355·0	327·7	315·3
B	315·1	322·2	328·8	311·0	310·5	308·1
C	309·8	318·8	332·7	290·9	284·9	302·9
Difference between A and C	42·9	16·1	0·8	64·1	42·8	12·4
			Height Increment (cm.)			
Illness						
A	40·9	38·7	37·1	40·1	37·6	35·3
B	39·7	37·7	35·1	41·6	35·8	36·4
C	37·6	34·9	35·8	36·7	35·4	34·4
Difference between A and C	3·3	3·8	1·3	3·4	2·2	0·9

TABLE 8
MEAN WEIGHT AND HEIGHT INCREMENTS AT TWO YEARS BY GRADE OF DIET

Birth Weight (lb. oz.)	Male			Female		
	4·8 and under	4·9 to 5·8	5·9 and over	4·8 and under	4·9 to 5·8	5·9 and over
Diet			Weight Increment (oz.)			
1	337	330	331	334	326	316
2	322	321	328	295	305	275
3	310	315	347	285	268	287
Difference between 1 and 3	27	15	−16	49	58	29
Diet			Height Increment (cm.)			
1	39·5	38·6	36·4	39·6	37·2	36·2
2	41·0	36·7	35·5	38·1	36·5	33·3
3	37·1	35·1	34·1	37·8	34·8	34·3
Difference between 1 and 3	2·4	3·5	2·3	1·8	2·4	1·9

TABLE 9
EFFICIENCY OF MOTHER BY BIRTH WEIGHT OF BABY

Birth Weight (lb. oz.)	Male			Female		
	4·8 and under	4·9 to 5·8	5·9 and over	4·8 and under	4·9 to 5·8	5·9 and over
Efficiency						
1	38·[illegible]	46·8	65·0	55·6	53·4	65·3
2	32·5	29·9	19·0	23·6	27·2	13·7
3	15·0	15·6	10·0	11·1	14·6	15·8
4	13·8	7·8	6·0	9·7	4·9	5·3
Total	100·0	100·0	100·0	100·0	100·0	100·0

TABLE 10
FREQUENCY OF ILLNESS BY BIRTH WEIGHT OF BABY

Birth Weight (lb. oz.)	Male			Female		
	4·8 and under	4·9 to 5·8	5·9 and over	4·8 and under	4·9 to 5·8	5·9 and over
Illness						
A	39·7	37·0	48·5	45·6	54·0	51·6
B	26·9	35·9	35·4	30·9	26·0	28·4
C	33·3	27·2	16·2	23·5	20·0	20·0
Total	100·0	100·0	100·0	100·0	100·0	100·0

TABLE 11
GRADE OF DIET BY BIRTH WEIGHT OF BABY

Birth Weight (lb. oz.)	Male			Female		
	4·8 and under	4·9 to 5·8	5·9 and over	4·8 and under	4·9 to 5·8	5·9 and over
Diet						
1	52·5	56·7	76·0	62·5	59·2	71·1
2	27·5	33·3	20·0	22·2	33·0	22·7
3	20·0	10·0	4·0	15·3	7·8	6·2
Total	100·0	100·0	100·0	100·0	100·0	100·0

mental conditions, a selected group has been extracted from the total premature sample, consisting of those who had a minimum of illness, a good diet and very good maternal care. No difference was found in mean weights when these selected prematures were further divided by social class of father, although as would be expected there was a predominance of children with fathers in social classes 1 and 2.

Fig. 1 shows the mean weights, from birth to 2 years, of selected premature infants who were 4½ lb. or less at birth, those who were between 4½ and 5½ lb. at birth, and the total control group of maturely born infants. By the age of 2 years the smallest singleton premature infants, both male and female, are only 14 oz. below the mean weight of

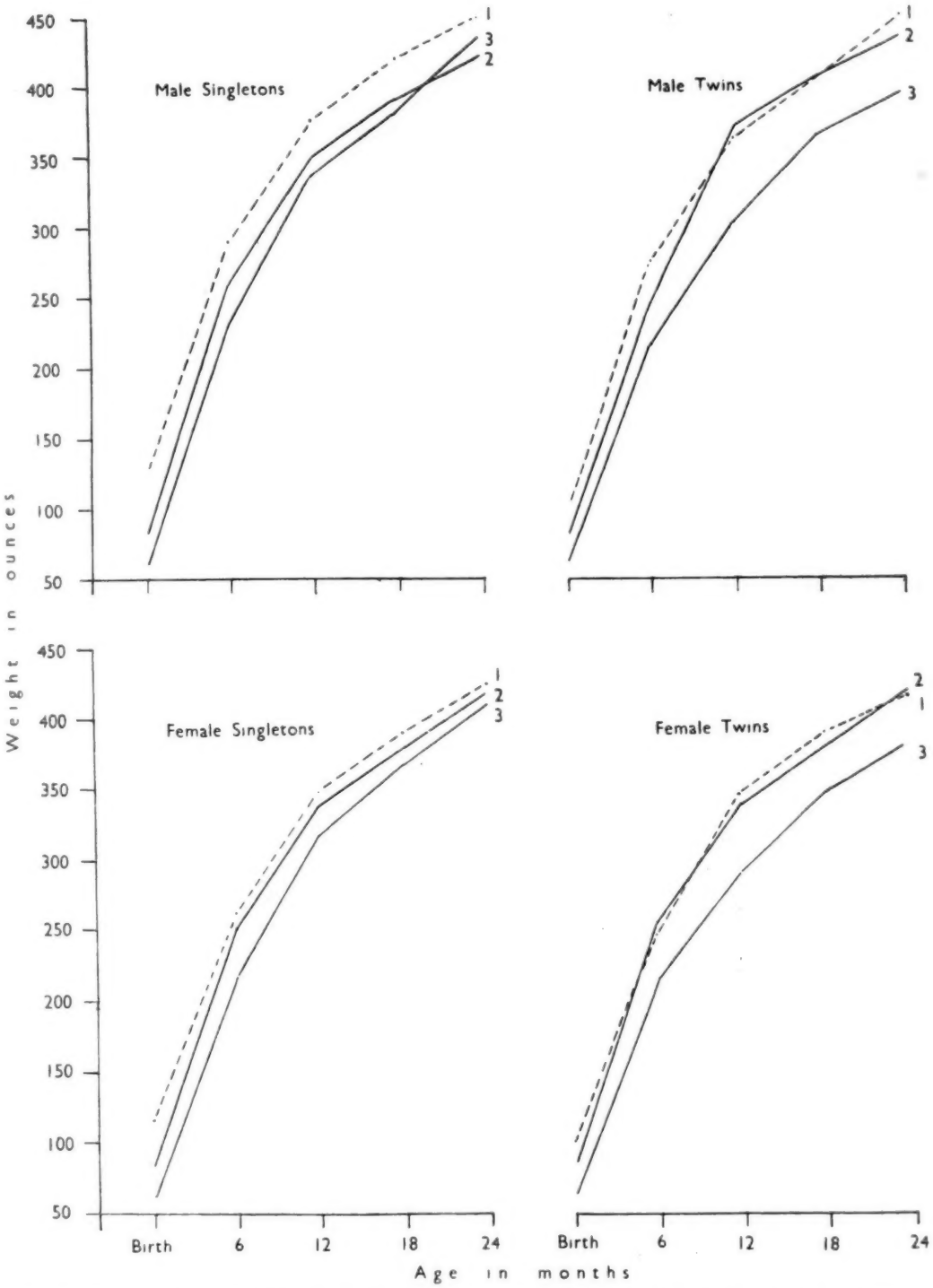


FIG. 1.—Mean weights of selected prematurely born children and mature controls. 1. Mature controls. 2. Premature: birth weight 4 lb. 9 oz. to 5 lb. 8 oz. 3. Premature: birth weight 4 lb. 8 oz. or less.

the mature controls, the differences at birth being 65 oz. for males and 55 oz. for females. However, in twin births those who were smallest at birth, even when given the best environmental conditions, are

still substantially behind the control group who were over 5½ lb. at birth, although those with a birth weight between 4½ and 5½ lb. have caught up with the control group.

In height, the selected prematurely born are very little behind the control group at 2 years except for twins who were less than 4½ lb. at birth, who show little reduction in their initial height handicap.

No significant correlation was found between length of gestation and 2-year weight increment. It might be expected that small babies born at term, often to mothers of small stature, would show a smaller weight gain after birth, but this was not obvious at 2 years. Douglas and Mogford (1953) also found no relationship between weight gain and gestation time.

In addition to the social factors already considered, one would expect growth to be influenced by genetic factors. In each case the height of the parents was recorded and those data included in the subsequent analysis.

Correlation and Regression Analysis

Tables 12 and 13 give the first order correlation coefficients between weight and height increments at 2 years and the following factors: mother's height, father's height, frequency of illness, the seven grades of illness frequency being used in this analysis, diet, maternal efficiency and social class of father. Two factors (mother's height and father's height) are presumably mainly genetic, and four (illness, diet, maternal efficiency and social class) are primarily environmental. The separation is not absolute. Heights of the parents will depend to some extent on diets in their own youth, and so will be partly socially conditioned. It was shown in a previous study, including these same women (Drillien, 1957), that mothers of premature babies are, on the whole, significantly shorter than mothers of mature controls and that average height was related to the woman's environment during childhood. The correlations will be reduced by imperfections in the assessment or measurement of the factor concerned. This is likely to affect in particular the social factors of diet and maternal efficiency which could only be approximately specified. The heights of mothers were recorded accurately during their stay in hospital, but a record of father's height was obtained by enquiry and is therefore less reliable. The correlation coefficients found may therefore be regarded as minimal and the true values, if they could be observed, would in general

TABLE 12

FIRST ORDER CORRELATION COEFFICIENTS BETWEEN WEIGHT INCREMENT AT TWO YEARS AND VARIOUS FACTORS

	Premature Singleton		Twins		Mature Singleton	
	Male	Female	Male	Female	Male	Female
No. of Cases	111	103	99	92	55	49
Weight Increment and:						
Mother's height	·1837	·4416	·2801	·3840	—·0162	·2966
Father's height	·2456	·3692	·2732	·3769	·3138	·2055
Illness	—·2368	—·3114	—·2830	—·3654	—·1446	—·2325
Diet	—·1482	—·3952	—·1974	—·3072	—·0771	—·2233
Mother's efficiency	—·1526	—·2905	—·2755	—·2942	·0790	—·1725
Father's social class	—·2011	—·2279	—·1234	—·2255	—·1601	—·2708
Baby's birth weight	—·1089	—·1064	·1408	·1572	—·0092	·1238
Minimum value for significance at 5% point	·1867	·1939	·1978	·2053	·2656	·2815

TABLE 13

FIRST ORDER CORRELATION COEFFICIENTS BETWEEN LENGTH INCREMENT AT TWO YEARS AND VARIOUS FACTORS

	Premature Singleton		Twins		Mature Singleton	
	Male	Female	Male	Female	Male	Female
No. of Cases	109	102	98	90	54	48
Length Increment and:						
Mother's height	·2890	·3777	·3082	·1702	·5020	·4504
Father's height	·3045	·3423	·1567	·2350	·3106	·3229
Illnesss	—·2345	—·1549	—·2215	—·2272	—·3439	·0592
Diet	—·1414	—·2336	—·2132	—·0708	—·0533	—·3196
Mother's efficiency	—·2354	—·1941	—·2999	—·2097	—·1764	—·1959
Father's social class	—·2045	—·1361	—·1621	—·2404	—·2537	—·1233
Baby's birth weight	—·2616	—·2816	—·3335	—·1890	—·1983	—·1118
Minimum value for significance at 5% point	·1884	·1949	·1988	·2706	·2680	·2845

be higher. Tables 12 and 13 indicate that the correlations between weight and length increments, and the genetic factors are comparable in magnitude to those with the social factors. In the premature and twin groups there is good concordance, the differences observed being within the expected range of random fluctuation. Not all the individual coefficients are statistically significant, but joint tests combining the four groups of male and female prematures and twins, show that the overall significance is beyond question for each of the separate genetic and social factors. As noted previously, the prematurely born singletons show a negative correlation between birth weight and weight increment, whilst the twins show a positive correlation indicating that there is a tendency for the singleton prematures to reduce their initial weight handicap by 2 years, though in the case of twins the reverse applies. However, in no case is the correlation coefficient significant at the 5% point. When height increment is considered, a negative correlation between length at birth and height at 2 years is found for all groups of singletons and twins, and taken together these findings are statistically significant. In the mature groups numbers are smaller and the significance of results thereby lowered.

In general, social factors appear to be relatively less important and genetic factors more so in those mature at birth. Of the social factors studied, frequency of illness gives the highest and most consistent correlations in the premature and twin groups. This is no doubt due to the fact that greater accuracy was possible in recording these data than for the other social factors, except for social class which *per se* seems of least importance in determining rate of growth. The various social and genetic criteria are not independent of one another. To disentangle the relative contributions of the different factors, extensive use has been made of the techniques of multiple correlation and regression analysis. For this it was necessary first to find the correlation of each of the factors employed with all the others. Table 14 gives these correlations and levels of significance.

Mother's height is quite highly correlated with father's height in each group, indicating a fairly high degree of assortative mating. Parental heights are also correlated significantly with all the social factors excepting frequency of illness. Frequency of illness is correlated with diet, social class and maternal efficiency, the last correlation, about ·5, being very high. Diet is correlated highly with social class and very highly with maternal efficiency, the values being about ·45 and ·75. Many multiple regressions were computed relating weight and length increment to various combinations of the genetic and social factors listed in Tables 12 and 13. In general, a combination consisting of mother's height (M), father's height (F) and one or two of the social factors will give significant, or near significant, regression coefficients for all factors included, but the most significant social factor varies in the different groups of infants. This is not surprising, for, as Table 14 shows, all social factors are quite highly intercorrelated among themselves. Each one is a more or less adequate partial measure of the others. The social factor which most often gave

TABLE 14

CORRELATION COEFFICIENTS BETWEEN THE VARIOUS GENETIC AND SOCIAL FACTORS EMPLOYED IN THE ANALYSIS

	Premature Singletons		Twins		Mature Singletons	
	Male	Female	Male	Female	Male	Female
No. of Cases	111	103	99	92	55	49
Mother's Height and:						
Father's height	·2581	·5093	·4392	·3809	·2321	·4958
Illness	−·0404	−·1390	−·1303	−·1930	−·0384	−·0633
Diet	−·2070	−·2236	−·2713	−·3595	−·0554	−·2399
Mother's efficiency	−·1718	−·2888	−·2991	−·3175	−·2510	−·2048
Father's social class	−·2079	−·2232	−·1760	−·2740	−·2218	−·1107
Father's Height and:						
Illness	−·0350	−·0857	−·1783	−·2693	−·0402	−·3512
Diet	−·2008	−·2036	−·4063	−·3670	−·1472	−·2260
Mother's efficiency	−·1610	−·1968	−·3466	−·4195	−·1122	−·2983
Father's social class	−·1867	−·2006	−·3504	−·2447	−·1337	−·2722
Illness and:						
Diet	·2405	·4263	·3894	·4656	·4500	·5404
Mother's efficiency	·5335	·4962	·5204	·4414	·4483	·4962
Father's social class	·2657	·2837	·3136	·1251	·3305	·5275
Diet and:						
Mother's efficiency	·7676	·7210	·7805	·8362	·7464	·7201
Father's social class	·5291	·3745	·4603	·4673	·3965	·4188
Mother's efficiency and:						
Father's social class	·5369	·4142	·5275	·5342	·4432	·5344
Minimum value for significance at 5% point	·1867	·1939	·1978	·2053	·2656	·2815

the highest regression coefficient, in combination with parental heights, was frequency of illness (I). The regression coefficient for the combination of three factors, M, F and I, is shown in Table 15. Column 1 shows the regression coefficients when all variates are scaled so that the standard deviations are unity. These are strictly comparable with the correlation coefficients set out in Tables 12 and 13, and indicate what the correlation between weight or length increment and the particular factor would be if the other factors were held constant. Column 2 gives the F tests of significance for these coefficients. A figure of 4 or more indicates significance at the 5% level. Column 3 gives regression coefficients in terms of the actual measurement. These figures give the average excess weight increment in ounces, or height increment in centimetres, per inch extra height in mother or father, and per unit decrease in the grading scale for illness. In weight one would expect an increased increment of about 4 oz. for every extra inch in mother's height, 3 oz. for each extra inch in father's height and ½ lb. decrease in weight increment for each increase in illness frequency grading from one to seven.

The standard deviation for maternal height is about 2·4 inches and for paternal height about 2·9 inches, the range of mother's height being 10 inches, and 12 inches for fathers (i.e., 95% of the heights are included in the range mean height ± 2 S.D.). Therefore one would expect a difference in weight increment at 2 years of about 40 oz. between children of the shortest and tallest mothers, rather less between the children of the shortest and tallest fathers, and 3½ lb. between those in the lowest and highest illness frequency grades. Similarly in height, one would expect an increased increment of about ·7 cm. for every extra inch in mother's height, ·4 cm. for every extra inch in father's height, and 1 cm. decrease in height increment for each increase in illness grade.

In spite of the inevitable fortuitous variation between the comparable coefficients there is a consistent picture. Whether for weight or height increment the primarily genetic factors (M and F) and the representative environmental factor (I) have a significant influence when the other type of factor has been fully taken into account. Perhaps the best way of expressing this is to work out the partial multiple correlation coefficients as shown in Table 16. These give the multiple correlations between weight or length increment and (1) Mothers' and fathers' heights, when all social factors are held constant. (2) Social factors (illness, diet and maternal efficiency), when parental heights are held constant.

It is evident that these partial coefficients are comparable in magnitude, with the genetic coefficients on the whole rather higher. Considering that parental heights themselves contain a social component and that the correlations with social factors are more likely to be attenuated by unavoid-

TABLE 16
PARTIAL MULTIPLE CORRELATION COEFFICIENTS

	Singleton Premature		Twins	
	Male	Female	Male	Female
Weight Increment and:				
Parental heights*	·2601	·4359	·2683	·3665
Social factors†	·2484	·3846	·2584	·2811
Length Increment and:				
Parental heights*	·3697	·3792	·2500	·1896
Social factors†	·2581	·1602	·2530	·2990

* Parental heights held constant † Social factors held constant.

TABLE 15
COEFFICIENTS FOR MULTIPLE REGRESSION OF WEIGHT OR LENGTH INCREMENT ON PARENTAL HEIGHT AND FREQUENCY OF ILLNESS

	1 Regression Coefficients in Standard Measure (partial Correlations)			2 F Values for Regression Coefficients			3 Regression Coefficients in Units of Measurement (Increment per inch height)		(Increment per illness grade)
	M	F	I	M	F	I	M	F	I
Premature Singletons:				Weight Increment at 2 Years (oz.)					
Males	·1214	·2065	−·2247	1·682	4·868	6·166	2·2333	3·1556	− 8·6743
Females	·3099	·1898	−·2520	9·731	3·695	8·626	5·4279	2·9282	−11·7322
Twins:									
Males	·1834	·1513	−·2321	3·053	2·047	5·866	3·1632	2·5719	− 8·7757
Females	·2538	·2102	−·2598	6·584	4·352	7·487	4·0116	2·8555	− 8·6260
Premature Singletons:				Length Increment at 2 Years (cm.)					
Males	·2271	·2452	−·2253	6·330	7·379	6·604	·7055	·6272	− 1·4576
Females	·2608	·2004	−·0994	5·942	3·558	1·159	·8629	·5806	− ·8702
Twins:									
Males	·2868	−·0013	−·1885	7·179	·0002	3·718	·9597	−·0043	−1·3884
Females	·0764	·1581	−·1637	·469	1·916	2·269	·2394	·4264	−1·0809

able inaccuracy of the assessments, it may be fairly concluded that in the groups studied genetic and environmental factors are of approximately equal importance in their influence on growth, whether measured by weight or by length increment during the first 2 years.

In few studies of the growth of prematurely born children has attention been paid to social background. Hess, Mohr and Bartelme (1934), using a control group of siblings, found that prematurely born boys had caught up in weight and height by 3 years, and girls somewhat earlier, except for those who were less than 3¼ lb. at birth. They point out that these children were all specially supervised from birth unlike the control group. Thirty per cent of their premature sample were first born and had no controls. Douglas and Mogford (1953) found that their premature group were lighter and shorter than their controls at 4 years. The mothers of those prematures who caught up or surpassed the controls by 4 years were taller and heavier than the mothers of those who failed to catch up. They conclude that the height of the mother gives the best indication of the likely growth pattern of her premature baby and that the small size of certain prematurely born children is genetically determined.

Summary

A statistical analysis is presented of a study of physical growth, in the first 2 years of life, in a group of 600 premature and maturely born children, including 200 twin births. The following conclusions were reached:

Throughout the 2-year period mean weights are closely related to mean birth weight. The smallest prematurely born singletons show a small increase in weight increment at 2 years. The smallest twins show a smaller weight increment, but neither finding is statistically significant.

In height, those largest at birth maintain their height superiority at 2 years, but there is a significant excess height increment in those smallest at birth.

Boys show a greater weight increment at 2 years than girls. There is little difference between the sexes in height increment.

Rate of growth whether measured by weight or height increment is affected by certain environmental factors. Substantially higher increments are recorded when maternal efficiency and diet are considered to be good, and frequency of illness is minimal. Environmental factors appear to exert a more marked influence on growth in the prematurely born than in the mature controls. In all premature groups there is a striking excess of inefficient mothers, poor diet and frequent illness.

Prematurely born singletons reared in the most favourable environmental conditions have very nearly caught up with the mature group in both weight and height by 2 years. This applies also to twins who were over 4½ lb. at birth, the smaller twins still being substantially behind the control group.

Genetic factors as deduced from parental heights also have an influence on rate of growth. Genetic and environmental factors were intercorrelated to quite a high degree. Using the technique of correlation and regression analysis it was found that genetic and environmental factors are of approximately equal importance in their influence on growth whether measured by weight or height increment at 2 years.

It is a pleasure to thank my secretary and research assistant, Miss A. E. Moore, Dr. Barnet Woolf who gave advice on the statistical analysis and Professor R. W. B. Ellis for his interest and encouragement throughout.

This research programme is being supported by a grant from the Scottish Hospital Endowments Research Trust.

References

Douglas, J. W. B. and Mogford, C. (1953). *Arch. Dis. Childh.*, **28**, 436.
Drillien, C. M. (1957). *J. Obstet. Gynaec. Brit. Emp.*, **64**, 161.
—— (1958). *Arch. Dis. Childh.*, **33**, 417.
Falkner, F. (1958). *Ibid.*, **33**, 1.
Hess, J. H., Mohr, G. J. and Bartelme, P. F. (1934). *The Physical and Mental Growth of Prematurely Born Children.* Chicago.
Lowe, C. R. and Gibson, J. R. (1953). *Brit. J. prev. soc. Med.*, **7**, 78.

PANCREATITIS IN YOUNG CHILDREN

BY

J. COLLINS

From the Roan Antelope Copper Mines, Luanshya, N. Rhodesia

(RECEIVED FOR PUBLICATION FEBRUARY 7, 1958)

Pancreatitis is rare in very young children and the medical literature contains comparatively few accounts of the associated pathology. The purpose of this paper is to describe the findings in the pancreas in four cases in which disease of this gland was discovered at autopsy and to discuss the pathogenesis of the condition. Three of the children concerned were Bantu of N. Rhodesia and were the only ones found to have pancreatitis in the routine examination of material from 100 consecutive autopsies on African children. The fourth child, included for comparison, was an Edinburgh girl and the only case of pancreatitis in the records of 1,812 consecutive post-mortem examinations conducted during the five years 1952-56 by the staff of the Pathology Department of the Royal Hospital for Sick Children, Edinburgh.

Case Histories

Case 1. A female Bantu child, aged 18 months and weighing 13 lb. 4 oz., was admitted to the African Hospital, Luanshya, where she was found to have bronchopneumonia, diarrhoea and vomiting (of several days' duration) with marked dehydration and kwashiorkor of moderate severity. She responded well to treatment but relapsed on the eighth day with further vomiting and diarrhoea for which she again required parenteral fluids. Soon after resuming oral feeding she suddenly collapsed and died in less than three hours. At necropsy the typical appearance of an acute haemorrhagic pancreatitis was found with haemorrhage extending for a considerable distance in the retro-peritoneal tissues both proximally and distally to the pancreas. Fat necrosis was not obvious and no abnormality was present in gall bladder, bile ducts or the terminal portion of the main pancreatic duct. On microscopical examination of the pancreas, the most striking changes were in the interlobular ducts most of which were dilated, some to a remarkable extent, while many contained eosinophilic material which had completely occluded the lumen. This material had often a distinctly laminated appearance and was sufficiently soft to be readily cut by the microtome knife, although tearing of the tissues in the immediate vicinity had occurred in some instances (Fig. 1). The epithelium lining some of these occluded ducts was unusually tall and columnar, and was occasionally more than one cell layer in thickness, but squamous metaplasia was not present in any of numerous sections examined.

In a few ducts rupture of the wall had occurred with herniation of the contents and in these situations there was a varying degree of round cell infiltration, many of the cells being polymorphs, but elsewhere the dilated and occluded ducts did not appear to have excited any significant reaction, only a very few lymphocytes being found in their walls and immediate surroundings. The main pancreatic duct was normal.

Haemorrhage, although widespread, was confined

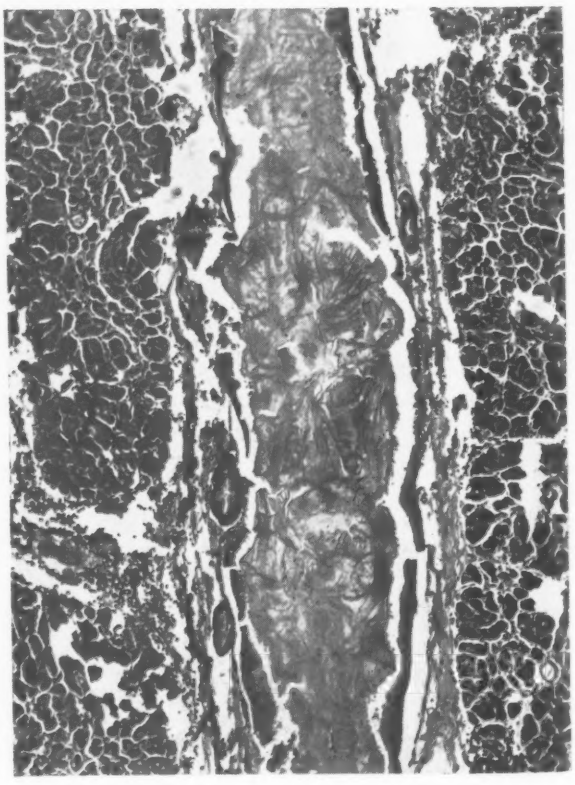


FIG. 1.—Case 1. Dilated and ruptured intralobular duct filled with inspissated secretions. (H. and E. × 70.)

mainly to the interlobular septa and the external pancreatic surface, where too the early changes of fat necrosis were present. The walls of a few vessels close to ruptured ducts showed the partial necrosis described by Rich and Duff (1936).

Apart from a few small foci of necrosis near ruptured ducts, the gland parenchyma and islets of Langerhans showed no abnormality except in one area where there had been former destruction and healing by fibrosis was occurring (Fig. 2) and in which the remains of ducts and

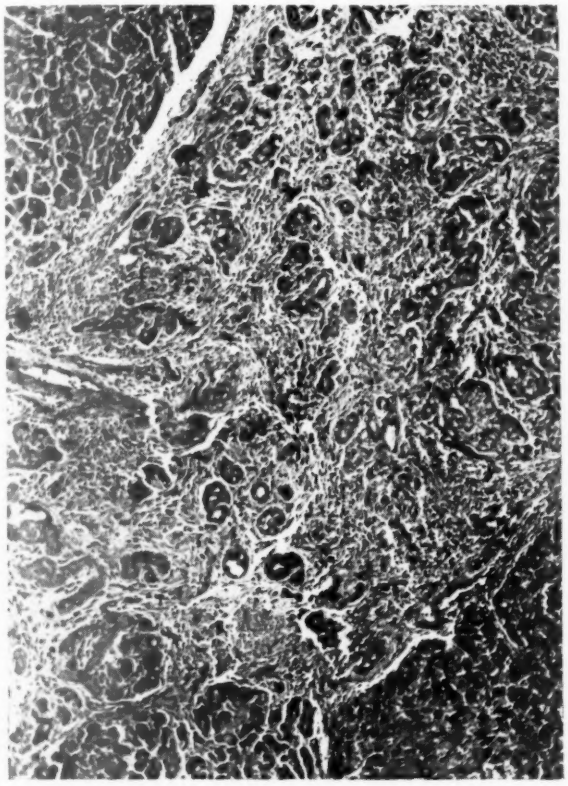


FIG. 2.—Case 1. Healing by fibrosis of an area of former destruction. (H. and E. × 70.)

eosinophilic material could, with difficulty, be distinguished.

Case 2. (71/53. Edinburgh). She was aged 2 years 9 months, and was under treatment for scalds involving 30% of the body surface. After some initial difficulty she had responded satisfactorily for 10 days; she then suddenly developed abdominal distension and vomiting, became shocked and collapsed, and, in spite of all attempts to improve her condition, died in 48 hours. Her previous history included hospitalization at 6, 9 and 14 months of age for persistent vomiting for which no cause was discovered. At autopsy an extensive pneumonia was present and some excess of free fluid in the abdomen. The pancreas appeared normal, but microscopic examination revealed an acute haemorrhagic pancreatitis, very similar in appearance to that of Case 1, but with less haemorrhage. The interlobular ducts were dilated and occluded by eosinophilic, laminated material (Fig. 3) and some had ruptured, but the duct epithelium showed neither hyperplasia nor metaplasia.

Case 3. A Bantu girl, aged 2 years and weighing 14 lb. 4 oz., was admitted to hospital at Luanshya with a history of convulsions for 24 hours and diarrhoea and vomiting

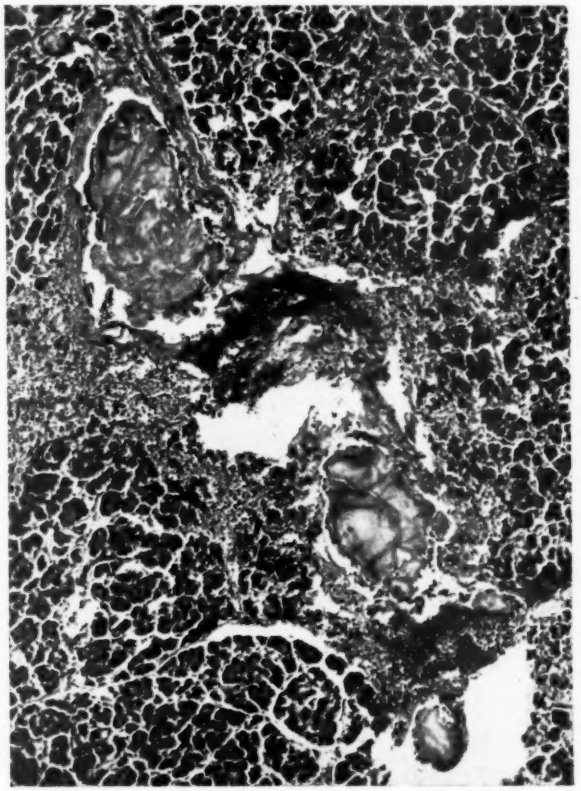


FIG. 3.—Case 2. Dilated and ruptured intralobular duct filled with inspissated secretions. (H. and E. × 70.)

for six or seven days. She was unconscious, very dehydrated, had a severe pneumonia with marked respiratory distress and died shortly after admission. At autopsy a confluent bronchopneumonia was found with numerous pin-head-size abscesses, subsequently shown to be staphylococcal in origin. There was no meningitis. The pancreas appeared unduly pink, but no actual haemorrhage was noted and no abnormality of the gall bladder, bile ducts or the terminal portion of the main pancreatic duct. Microscopically sections from the body of the pancreas showed many dilated interlobular ducts occluded by eosinophilic material similar in all respects to that already described. Some of these ducts had ruptured with partial herniation of contents, and in these areas round cell infiltration was evident (Fig. 4). The duct

epithelium was of normal appearance as was the main pancreatic duct. In a few areas some dilatation of pancreatic acini and ducts was present without duct occlusion being found.

Case 4. A Bantu girl, aged 2 years and weighing 18 lb., was admitted to the African Hospital, Luanshya, with bronchopneumonia, moderately advanced kwashiorkor with oedema of the feet and legs and some areas of skin exfoliation, and also severe gastro-enteritis. After initial improvement she developed thrombocytopenic purpura and rapidly succumbed to intestinal haemorrhage.

At autopsy the presence of bronchopneumonia, purpura and intestinal haemorrhage was confirmed, but the pancreas appeared to be normal. Microscopically sections of the lungs showed a giant-cell pneumonia. Sections of the body of the pancreas showed a small, completely disorganized area, with foci of necrosis surrounded by dilated and partly necrotic acini. Early fibroblastic proliferation was present and a patchy round cell infiltration. A few severely damaged ducts were recognizable and seemed to be occluded by eosinophilic material. Staining with P.A.S. simplified recognition of these ducts and one is shown in Fig. 5.

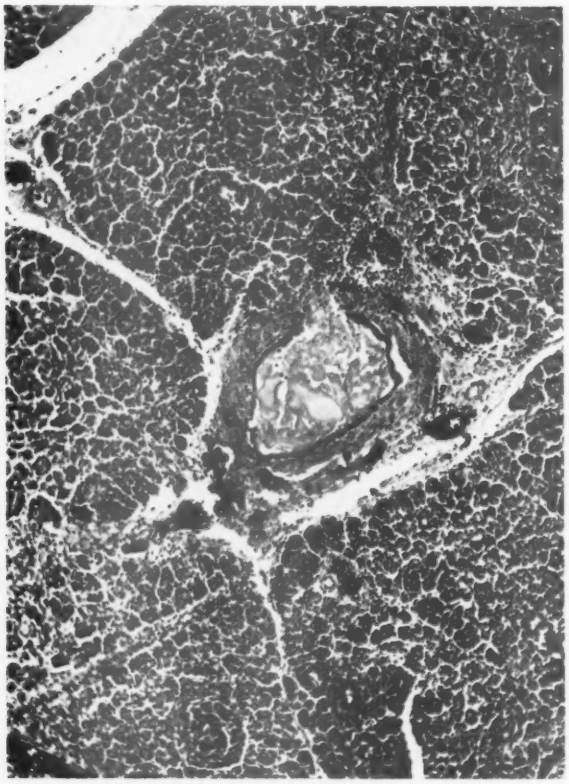


FIG. 4.—Case 3. Dilated and ruptured intralobular duct filled with inspissated secretions. (H. and E. × 70.)

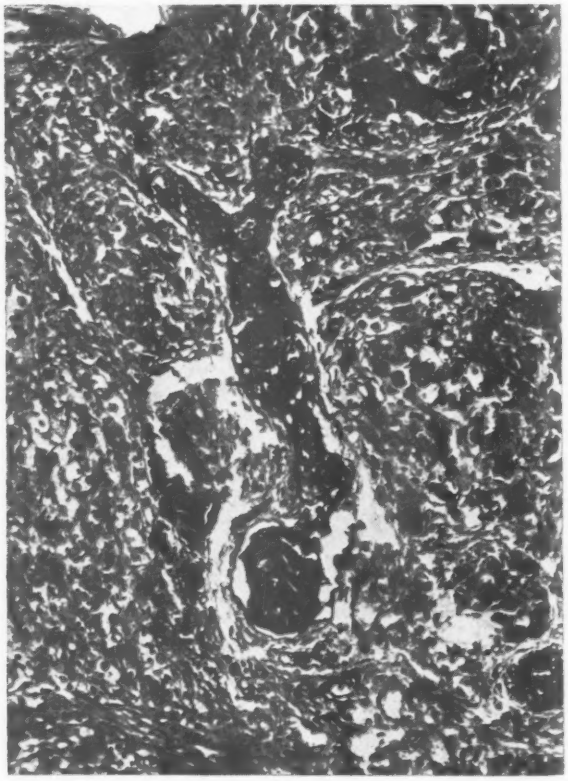


FIG. 5.—Case 4. Severely damaged duct, filled with inspissated secretion, in area of destruction. (P.A.S. × 120.)

Comment

The pathology in Cases 1 and 2 was that of a typical acute haemorrhagic pancreatitis, while that in Case 3 was of lesser severity. In the pancreas of Case 1, however, there was also a small scarred area from a previous incident, not yet completely healed, and Case 4 showed the picture of a similar area at a much earlier stage.

In the first two cases, death was due to the pancreatic condition and this too may have contributed to the fatal outcome in the third, although the pneumonia alone was sufficient to have caused the death of the child. The very small focus of healing pancreatic damage found in Case 4 cannot be regarded as other than an incidental finding.

Discussion

Our knowledge of the pathogenesis of acute haemorrhagic pancreatitis was considerably extended by the work of Rich and Duff (1936) and since that date many others have stressed the

importance of the mechanical factor in the initiation of this condition. In Rich and Duff's series of cases this factor was duct occlusion caused by epithelial hyperplasia and metaplasia, but they also mention three cases in which inspissated secretions, staining irregularly with eosin, were present and which were sometimes associated with inflammatory signs in the walls of the affected ducts.

More recently, Wainwright (1951) found, in the routine examination of material from 2,500 autopsies on persons over 25 years of age, four instances in which inspissated material alone was present in pancreatic interlobular ducts and 81 others in which it was associated with duct epithelial hyperplasia; he suggested that the presence of this material could contribute to duct obstruction. As there can be little doubt that the intraductal material in the four cases presented here did in fact cause duct obstruction it seems worthwhile to discuss the nature and probable cause of these eosinophilic plugs.

In these four cases, the absence of any significant tissue reaction in the vicinity of affected ducts, except where rupture has occurred, and the general similarity of the appearance of the intraductal material to that found in cases of fibrocystic disease of the pancreas, seems to confirm that these eosinophilic plugs are in fact inspissated secretions; moreover their somewhat laminated appearance points to formation over a period of time with enlargement occurring at intervals.

Andersen (1938), referring to similar material, believed that its formation was due to a disturbance of the autonomous nervous stimulation of glandular pancreatic secretion and Baggenstoss (1948) thought that such inspissation could be caused by vagal stimulation, dehydration and possibly malnutrition, especially protein deficiency.

That vagal stimulation does result in the formation of an unnaturally thick and viscid pancreatic juice, rich in enzymes, is a known physiological fact but that protein deficiency can exert a similar effect must be regarded as doubtful, for in kwashiorkor, a disease of protein deficiency the pathology of which has been extensively studied, inspissated pancreatic secretions are very infrequently found (Trowell, Davies and Dean, 1954) and the main pancreatic lesion is a loss of zymogen granules and collapse of the acinar cells (Davies, 1948), a condition hardly compatible with the production of viscid secretion.

The formation of these plugs may be connected with dehydration as the presence of slightly dilated ducts filled with eosinophilic secretions is a common finding in children and others dying in a dehydrated state (Bodian, 1952). Fig. 6 shows a portion of pancreas from such a case and it is possible that in certain circumstances such pools of secretion may become inspissated and form pancreatic ductal obstructions.

In Central Africa, dehydration in children is most often the result of diarrhoea and vomiting which, at certain seasons of the year, is so widespread that most young African children are affected and many at such frequent intervals that the weights recorded for Cases 1, 3 and 4 are by no means unusual. Since vomiting and diarrhoea may be expected to give rise to vagal stimulation as well as dehydration, the combination of these factors should result in the formation of an abnormally viscid pancreatic secretion. Furthermore, children suffering severely from diarrhoea and vomiting usually refuse all food, and few African mothers in such circumstances would make any effort to coax them to take anything other than perhaps a little water, thereby removing any stimulus for the pancreas to commence the production of more normal secretions to wash out the unnaturally thick and viscid material present in the ducts.

It seems reasonable to assume that if such a state of affairs continued over a period of days, as it

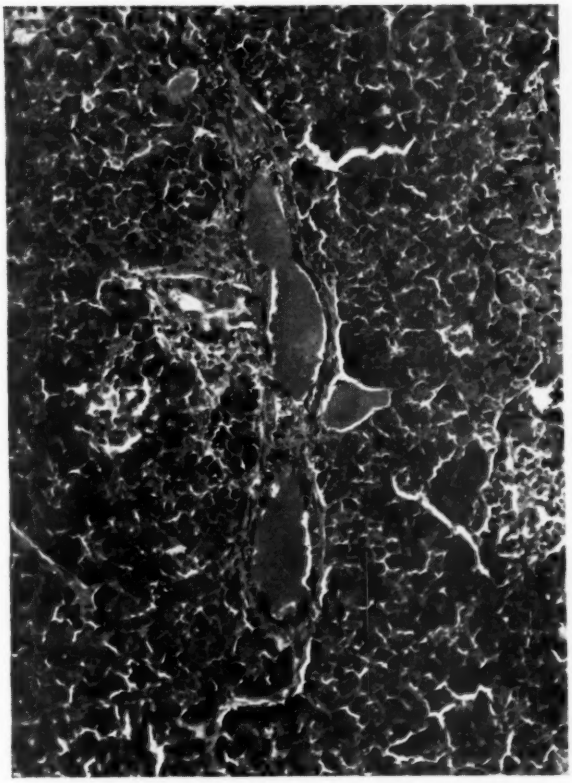


FIG. 6.—Pooled secretions in intralobular duct of a child dying from gastro-enteritis and dehydration. (H. and E. × 120.)

frequently does, inspissation would occur and the seed be sown for future pancreatic damage.

Once inspissation is present it is probable that further deposition would follow, as occurs for example in the case of renal calculi, particularly on any fresh occurrence of similar circumstances, so giving rise to the laminated appearance of the deposit as well as the dilatation and finally obstruction of the affected ducts.

Such a mechanism could account for the occluded ducts found in all three Bantu cases and probably too for those in the Edinburgh child, whose early history contains episodes of persistent vomiting requiring admission to hospital on three occasions. It is also probable that in the latter case her scalds gave rise to some degree of dehydration, as well as vagal stimulation, which may have added to inspissations already present.

Once duct obstruction has occurred rupture is probably inevitable sooner or later, but that the resulting pancreatitis can be confined to a very small area is illustrated in Cases 1 and 4 and the detection of such minute lesions on naked eye examination may be impossible.

If this theory of the cause of these intraductal obstructions is correct then, apart from the normal procedures to remedy dehydration, other measures to overcome vagal stimulation (where this is present) and to encourage normal pancreatic secretions are indicated in all very young sick children.

Summary

The pathology in four cases of pancreatitis in children is described and illustrated.

In each instance inspissated secretions had caused the dilatation, obstruction and subsequent rupture of intralobular ducts and in two cases the resulting pancreatitis had been confined to a very small area and was undergoing healing by fibrosis.

It is suggested that this inspissation is brought about by a combination of vagal stimulation, dehydration and the absence of normal pancreatic secretions over a period of time probably measured in days.

My thanks are due to Dr. A. C. Fisher, O.B.E., Chief Medical Officer of the Roan Antelope Copper Mines Ltd., for permission to publish this paper; Dr. Agnes R. Macgregor, Consulting Pathologist to the Royal Hospital for Sick Children, Edinburgh, for access to her records and the material for Case 2; Dr. R. F. Ogilvie, Consulting Pathologist, Royal Infirmary, Edinburgh, for much helpful advice and to Mr. T. C. Dodds, of the Medical Photographic Unit, University of Edinburgh, for the photographs.

References

Andersen, D. H. (1938). *Amer. J. Dis. Child.*, **56**, 344.
Baggenstoss, A. H. (1948). *Arch. Path. (Chicago)*, **45**, 463.
Bodian, M. (1952). *Fibrocystic Disease of the Pancreas.* London.
Davies, J. N. P. (1948). *Lancet*, **1**, 317.
Rich, A. R. and Duff, G. L. (1936). *Bull. Johns Hopk. Hosp.*, **58**, 212.
Trowell, H. C., Davies, J. N. P. and Dean, R. F. A. (1954). *Kwashiorkor*, p. 148. London.
Wainwright, C. W. (1951). *New Engl. J. Med.*, **244**, 161.

HERPES ZOSTER OPHTHALMICUS IN CHILDREN

BY

S. M. TUCKER*
From St. Andrew's Hospital, Bow, London

(RECEIVED FOR PUBLICATION JANUARY 30, 1958)

Herpes zoster ophthalmicus, first described fully by Jonathan Hutchinson in 1866, is very rare in children, being predominantly an adult affection (Doggart, 1933; Björk, 1950; Duke-Elder, 1952). Koch (1939), in reporting a case in a child of 5½ years of age, states that only one other child, aged 12, developed zoster ophthalmicus at the Mayo Clinic before 1938. In a fairly exhaustive analysis of the literature by Poulsen (1955) only 17 cases had been reported in children, three of whom had the disease within the first year of life. Poulsen adds his own contribution, that of a boy of 15 months. Several standard text books (Mitchell Nelson, 1954; Cecil and Loeb, 1951; Price, 1956) make little or no mention of herpes zoster ophthalmicus in infants and children.

Edgerton (1945), in a detailed analysis of herpes zoster ophthalmicus, found about 2,250 cases in the world literature. The average age of these cases was 43 years. He could only find 44 cases under 13 years of age, but did not attempt to differentiate between the epidemic or symptomatic forms. He does, however, state that in the vast majority of cases of ophthalmic zoster, the disease was secondary or symptomatic.

In view of the great deal of evidence which has accumulated recently linking the virus of herpes with that of chickenpox (Bokay, 1909; Brain, 1933; Amies 1934; Weller, 1953; Simpson, 1954; Blank and Rake, 1955) it is surprising to find so few authenticated cases of herpes zoster in children, while chickenpox is such a common and highly infectious exanthema. Chickenpox has its maximum incidence in childhood, whereas herpes is more commonly observed from the ages of 20 to 65 years. Edgerton (1945), on the other hand, quotes Evans and Fox (1905) as saying that herpes zoster ophthalmicus was common in the young. They state that one half of their patients were under 14 years of age. Cases of ophthalmic zoster in children have been reported by other authors as well, but few detailed descriptions can be found in the British literature. Roll (1920), presenting the case of a child of 3 years, commented on the unusually early age for such a condition.

The following typical case appears to be one of the few documented cases in the British literature of epidemic herpes zoster ophthalmicus affecting the first division of the trigeminal nerve in a child.

Case History

D.T., a boy aged 6 years, admitted on July 17, 1956, was the fourth child of healthy parents. He had a normal infancy except for frequent bouts of tonsillitis from the age of 2 years which usually improved without treatment. Tonsillectomy was finally resorted to during June, 1955. He also had a bout of diarrhoea earlier in 1955 but this was very mild. He had mumps, measles and whooping cough during infancy and chickenpox in 1952. Three of the other four children had all had chickenpox many years previously and none of them had had herpes zoster at any time. There was no recent history of having been in contact with herpes or chickenpox.

The boy's present illness began four days before admission to hospital, when his main complaints were of abdominal pain and headache. He was kept in bed and observed.

Three days before admission, he began to complain of pain over his left eye associated with mild photophobia. For the following three days he was pyrexial with a temperature range of 99°-100°F., vomited on a few occasions and still complained of abdominal pain and headaches. The pain over his left eye had now become more acute and the child was subsequently admitted for investigation.

On examination his general condition was good but the temperature was raised to 99°F. He was reluctant to eat and vomited up what was offered to him. His frontal headache was most painful at this stage but again there were no abnormal findings in any of the other systems. Careful daily examination did not reveal any rash or other abnormal physical findings but on the child's fourth day in hospital a mild conjunctivitis of the left eye was noted with some erythema around the eye. No oedema was present. There was no evidence of any vesicle formation.

On July 21, 1956, a classical cutaneous zoster affecting the ophthalmic branch of the left trigeminal nerve was observed which included the nasociliary branch on that

*Present address, Middlesex Hospital, London.

side (Fig. 1). The vesicles extended only to the midline and involved the left side of the forehead, both upper and lower eyelids, the left eyebrow, and the root of the nose on the left together with the bridge and the tip. Many of the vesicles had broken down. The left eye was now inflamed and swollen and the upper lid overrode the lower as the eye became closed. Conjunctivitis and iritis were also present. The pupil was inactive but the fundi and discs were normal. The vessels appeared engorged. Diffuse corneal oedema was also present with some impairment of sensation. The tension of the eye appeared normal. Two other vesicles were seen elsewhere on the trunk.

On July 22 the herpetic dermatitis had become infected and left keratitis was noted. Atropine 1% eye drops were instilled into the affected eye and aureomycin 1% ointment applied to the infected vesicles. The temperature had now risen to 103°F. and the child was extremely ill. Left pre-auricular adenopathy was present. The temperature remained high until July 25, when the ophthalmologist reported that iridocyclitis with punctate keratitis was present. It was decided to continue with atropine, and cortisone drops were added four-hourly.

Within a few days the temperature subsided to normal and the child appeared much happier. He began taking food adequately for the first time since the onset of his illness. The cutaneous herpes had improved considerably but it was noted that the hair on the left side of the head, at the upper limit of the ophthalmic division, had thinned considerably. The right eye remained normal throughout.

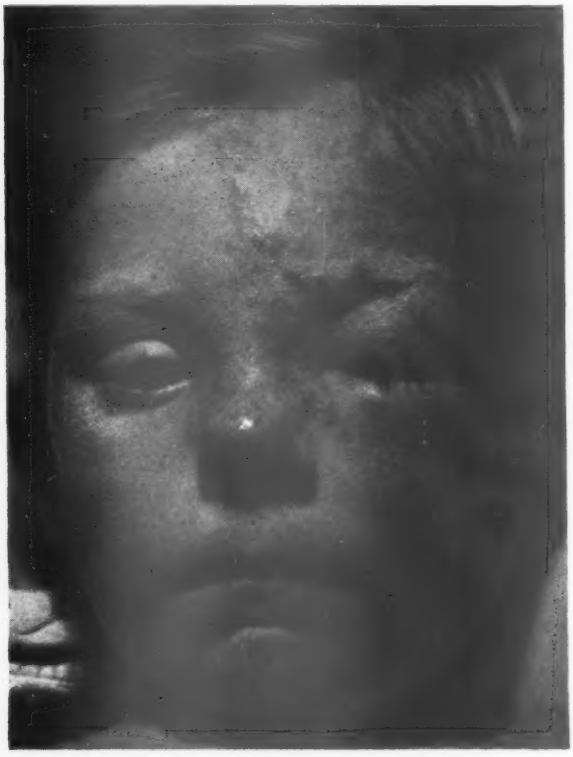


FIG. 1.

Progress continued and on August 1 the left eye was still mildly inflamed but the chemosis was distinctly less; there was marked ciliary injection and the cornea was very hazy. Typical deep spots were seen in the corneal stroma. Considerable punctate keratitis was present. The pupil was small and was not fully dilated on atropine.

On August 10 keratitis was still present. The eye had become whiter and the pupil was still not fully dilated. The corneal ulcers no longer stained up on fluoroscopy, but characteristic deep white spots were seen in the corneal stroma. Photophobia remained intense.

On August 14 the eye was a little improved, the pupil was wider and there were extensive central nebulae. No corneal sensation was detected. The chemosis and swelling had by this time completely resolved but the herpetiform scars were still evident. The hair was sparse on top but the rash had cleared up.

On September 26, about five weeks later, the cornea showed a ground glass appearance with a few deep residual corneal spots. One month later this had cleared and the corneal haze was noted to be gradually disappearing. No posterior synechiae were present.

In November, 1956, residual corneal dot opacities were still present. Vision in the left eye was only 6/60. The left pupil had now become eccentric. The hair on the forehead had begun to grow again but was still not normal.

Vision improved as the months went by and was found to be 6/36 in the left eye by February, 1957.

He was last seen in June, 1957, one year after the initial infection, when he was found to have supraorbital scarring, normal hair growth of the left forehead, and an eccentric left pupil. Vision had now improved to 6/9. He had been very well in himself for the past few months and had resumed schooling. Sensation in the left eye had returned to normal.

Discussion

Herpes zoster ophthalmicus usually follows a mild course in children, and it is the rule that all traces of the infection clear up with little residual damage. Ocular complications are usually mild and the children do not appear unduly perturbed by the disease. Post-herpetic neuralgia, so common in affected adults, rarely troubles the child (Björk, 1950).

This case differs from the general observations in some essential points. The child was extremely ill and toxic once the herpes became evident, most unlike many of the cases reported (Poulsen, 1955). Loss of hair in the ophthalmic division was very noticeable and this finding does not appear to have been commented upon much previously. Normal vision had not completely returned one year after the original illness, although improvement has been maintained.

Aetiologically, two types of herpes zoster ophthalmicus are described (Duke-Elder, 1952): (1) The epidemic form which is caused by a specific virus and produces a lesion in every way comparable with

herpes zoster elsewhere. This form is usually of sudden onset with severe constitutional disturbances such as fever, prostration and vomiting and these general signs often precede the neuralgic pain of the herpes. (2) The symptomatic form due to the involvement of the ganglion secondarily in infective, neoplastic or traumatic disturbances, e.g. syphilis, tuberculous meningitis or a pontine tumour. It may also be caused by drugs, e.g. arsenic or carbon monoxide poisoning. This form cannot be definitely diagnosed as such unless the patient shows other evidence of the causal agent, which may not appear until months or years later. Many of the cases reported in children may well be this symptomatic form with the evidence or cause of the trouble as yet not manifest.

The case described falls into the first group. Duke-Elder states that herpes zoster ophthalmicus of the epidemic type almost always affects adults and the aged; it runs a fairly similar course in all cases from onset to subsidence.

Doggart (1933) lists three principal features in the diagnosis of epidemic herpes zoster: (1) Pain along the course of distribution of the first division of the fifth cranial nerve; (2) A skin rash appearing about three days later on a portion of the corresponding area of the face or head; (3) Limitation of the rash to one side.

Ocular complications usually occur in about 50% of adults affected, the main ones being keratitis, iritis, scleritis, ocular muscle palsies and optic neuritis. If the naso-ciliary branch of the ophthalmic division of the trigeminal nerve is involved by a lesion of the tip of the nose, the eye will very often be involved as well (Hutchinson, 1866). This case illustrates the rule quite convincingly.

Relation of Herpes Zoster to Varicella. The virus causing herpes zoster is now believed to be identical with the virus of varicella and there is a large amount of clinical and experimental evidence for the association (Bokay, 1909; McEwen, 1920; Jacobi, 1921; Simpson, 1954; Blank and Rake, 1955).

Minor antigenic differences may be present but the two viruses appear to be very closely related. They may differ perhaps in the mode of attack by the virus: in herpes zoster spread is by the lymphatics, whereas in chickenpox it is usually via the blood stream (Low, 1919). There remains the possibility of the occurrence of two forms of epidemic herpes zoster, one allied to chickenpox and one allied to herpes. Most evidence, however, supports the monistic theory that zoster and chickenpox are different manifestations of infection by the same virus, zoster being usually a reawakening of the latent infection of chickenpox (Blank and Rake, 1955).

Simpson (1954) after studying an epidemic on the Shetland Island of Yell of ordinary varicella and also of varicella caught from a shingles contact on the same island, could find no distinction in the clinical manifestations, in the mean reproductive cycles, in the infectiousness of the disease or in the solidity of the protection conferred by a previous attack against varicella of the same or of the alternative origin, i.e. complete cross immunity, and concluded that the varicella caught from shingles is due to the same virus as ordinary chickenpox. He also showed that people infected with chickenpox derived from a case of zoster were subsequently immune for a few years to ordinary chickenpox infection; and similarly, people who had previously had chickenpox were not infected when exposed to the virus derived from a case of zoster.

Experimental evidence of Kundratitz (1925) and Bruusgaard (1932) as early as 1925 is in line with the views expressed by Simpson (1954) and they offer laboratory evidence of close similarities between the two aetiological agents.

Summary

Herpes zoster ophthalmicus is a rare form of herpes infection in children, being primarily an adult affection. A case of a boy of 6 years is presented who showed the classical unilateral eruption together with some other unusual features. The association of the herpes zoster virus with varicella is discussed.

I am indebted to Dr. B. D. R. Wilson under whose care the child was admitted for helpful advice and criticism and to Mr. L. M. Green for ophthalmological comments.

References

Amies, C. R. (1934). *Brit. J. exp. Path.*, **15**, 314.
Björk, A. (1950). *Acta derm.-venereol.* (*Stockh.*), **30**, 34.
Blank, H. and Rake, G. (1955). *Viral and Rickettsial Diseases of Skin, Eyes and Mucous Membranes of Man.* Boston.
Bokay, J. von. (1909). *Wien. klin. Wschr.*, **22**, 1323.
Brain, R. T. (1933). *Brit. J. exp. Path.*, **14**, 67.
Bruusgaard, E. (1932). *Brit. J. Derm.*, **44**, 1.
Cecil, R. L. and Loeb, R. F. (1951). *Textbook of Medicine.* London and Philadelphia.
Doggart, J. H. (1933). *Brit. J. Ophthal.*, **17**, 513.
Duke-Elder, S. (1952). In *Textbook of Ophthalmology.* Vols. II and V. London.
Edgerton, A. E. (1945). *Arch. Ophthal.* (*Chicago*), **34**, 40, 114.
Evans and Fox. (1905). *Brit. J. Derm.*, **17**, 199.
Hutchinson, J. (1866). *Ophth. Hosp. Rep.* **3**, 72; **5**, 191.
Jacobi, O. (1921). *Z. Kinderheilk.*, **29**, 368.
Koch, F. L. P. (1939). *Arch. Ophthal.* (*Chicago*), **21**, 118.
Kundratitz, K. (1925). *Wien. klin. Wschr.*, **38**, 502.
Low, R. C. (1919). *Brit. med. J.*, **1**, 91.
McEwen, E. L. (1920). *Arch. Derm. Syph.*, **2**, 205.
Nelson, W. E. (1954). In *Textbook of Paediatrics*, 6th ed. London and Philadelphia.
Poulsen, P. A. (1955). *Acta med. scand.*, **151**, 131.
Price, F. W. (1956). In *Textbook of Medicine*, 9th ed., London.
Roll, G. W. (1920). *Proc. roy. Soc. Med.*, **13**, 81.
Simpson, R. E. H. (1954). *Lancet*, **2**, 1299.
Weller, T. H. (1953). *Proc. Soc. exp. Biol.* (*N.Y.*), **83**, 340.

OBSERVATIONS ON THE BROMIDE PARTITION TEST IN THE DIAGNOSIS OF NON-PURULENT MENINGITIS

BY

V. S. NICOL and H. T. FAWNS

From the Paediatric Unit and Department of Pathology, Worcester Royal Infirmary

(RECEIVED FOR PUBLICATION FEBRUARY 10, 1958)

The Bromide Partition Test

In its earliest stages when treatment will produce the most favourable results, tuberculous meningitis may be difficult to diagnose clinically, since other infective non-bacterial conditions of the central nervous system may present a similar clinical picture at their onset.

Since the bromide partition test and its use in the diagnosis of tuberculous meningitis were described (Taylor, Smith and Hunter, 1954) we have found it a useful aid to diagnosis in six cases of tuberculous meningitis and 20 cases of non-tuberculous meningitis (Fig. 1).

Normally after oral or intravenous administration of sodium bromide, the ratio of serum bromide/cerebrospinal fluid bromide is above 1·65 (usual range 2-3). In cases of tuberculous meningitis the integrity of the blood cerebrospinal fluid barrier is affected and there is an early fall in the ratio below 1·65 towards unity, with a return to normal when the infection is brought under control. In other types of non-purulent meningitis a fall in the ratio does not occur. In cases of purulent meningitis this fall may, or may not, occur. In five cases of purulent meningitis described by Cheek (1956) there was a low ratio in two cases, in the other three the ratio was normal. Owing to the different clinical course of purulent meningitis, this type of test should not be necessary, and no cases of purulent meningitis are included in our series.

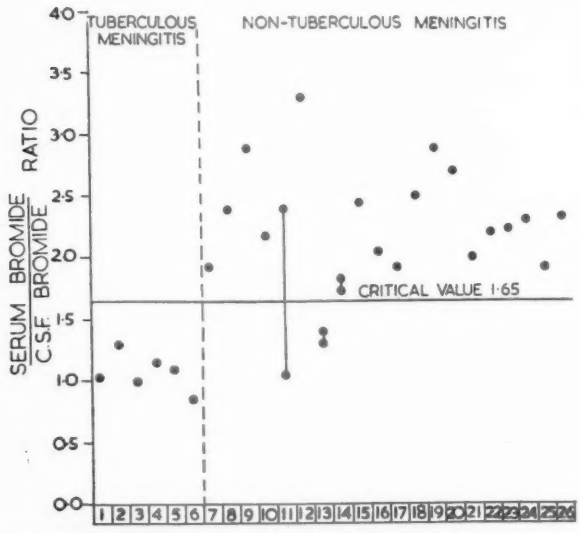


FIG. 1.—Scatter diagram of bromide partition test.

The method used is that described by Taylor, Smith and Hunter (1954). Sodium bromide is given orally, 0·25-1 g. t.d.s., for three days, or as a single intravenous injection of 2-8 g. (the solution contains 8 g. in 30 ml.). Venous blood, 5 ml., and lumbar cerebrospinal fluid, 8 ml., are collected 24 hours after intravenous, and 48 hours after oral administration, for bromide estimation. The authors of the original paper stress the importance of collecting lumbar cerebrospinal fluid as fluid obtained by cisternal or ventricular puncture yields different values.

Analytical Method

Bromide was estimated by the method of Hunter (1953) which is the technique of choice for this test as it enables the relatively small serum and cerebrospinal fluid levels to be estimated with greater accuracy than by other methods (Hunter, Smith and Taylor, 1954). This method is a quantitative application of the Van der Meulen reaction, whereby bromide is oxidized to bromate by hypochlorite. The excess hypochlorite is removed with sodium formate, after which the bromate liberates a corresponding amount of iodine from potassium iodide, which is titrated with N/200 sodium thiosulphate, using a starch indicator. The end point is sharp and satisfactory.

One ml. of serum or cerebrospinal fluid is required for each estimation.

In the majority of cases estimations were carried out in duplicate and the mean value reported. In a few cases, however, shortage of material made this impossible. It is essential to carry out a 'reagent blank' with each test, as there is a somewhat large and variable blank value arising from reagents, which must be deducted

TABLE 1

FIGURES FOR THE FIRST 10 DUPLICATED ANALYSES OF SERUM AND OF CEREBROSPINAL FLUID. SHOWING THE MEAN VALUES REPORTED AND THE DEGREE OF ACCURACY*

Specimen No.	Serum				Cerebrospinal Fluid			
	I	II	Mean	Accuracy (%)	I	II	Mean	Accuracy (%)
1	35·6	36·2	35·9	±0·84	13·0	13·4	13·2	±1·52
2	61·0	61·2	61·1	±0·16	65·0	63·0	64·0	±1·56
3	35·6	34·1	34·8	±2·21	32·0	29·6	30·8	±3·90
4	131·0	129·0	130·0	±0·77	5·8	5·8	5·8	±0·00
5	92·8	91·2	92·0	±0·87	26·4	27·4	26·9	±1·86
6	17·6	19·2	18·4	±4·30	18·5	19·5	19·0	±2·63
7	14·2	13·4	13·8	±2·90	24·7	24·7	24·7	±0·00
8	56·0	57·0	56·5	±0·89	27·7	25·7	26·7	±3·72
9	24·5	24·5	24·5	±0·00	5·7	3·8	4·75	†±20·0
10	19·7	19·5	19·6	±0·51	27·0	27·0	27·0	±0·00
	Accuracy: average ±1·35% (Range: 0·00–4·30%)				Accuracy: average ±1·69% (Range: 0·00–3·90%)			

* Results are expressed as bromine mg. %.

† Not included in calculating the average and range for this series. This much larger error is due to the difficulty in estimating the very small amount of bromine present.

from the serum and cerebrospinal values. Initially, the method involves ashing protein-free alcoholic extracts of serum and cerebrospinal fluid in nickel crucibles, but apart from these no special apparatus is required other than what is normally available in a clinical laboratory. The original method suggests that 4 ml. of alcoholic supernatant fluid be used for the estimation after protein precipitation. This is satisfactory for cerebrospinal fluid but in the case of sera we frequently found it difficult to realize this volume. As a routine, we therefore employed 3·5 ml. and corrected the calculation accordingly. The accuracy of the method appears satisfactory. From the point of view of a busy clinical laboratory, one might perhaps make the criticism that it is somewhat time-consuming.

Results are expressed as mg. % of bromine, and Table 1 gives the figures for the first 10 duplicated analyses, for serum and cerebrospinal fluid respectively. Some of these figures refer to adult cases of meningitis and are not dealt with in this paper. The accuracy is expressed as the percentage difference between the individual analyses and the mean value reported. Hunter (1953) claims an accuracy of approximately ± 1% for the method, and the majority of our own analyses agree with this. At the outset of this work, recovery tests were carried out with sodium bromide added to serum at a concentration of 10 mg. %, expressed as bromine. The recovery range was 97% to 104%, but it was possible to improve on this standard of accuracy with the higher concentrations encountered in the test specimens.

TABLE 2

Case No.	Serum Bromide (mg. %)	C.S.F. Bromide (mg. %)	Serum CSF Ratio	Mantoux 1·1000	Culture C. Guinea Pig G.	Cerebrospinal Fluid Findings			T.B. Family History	Diagnosis
						Cells (per c.mm.)	Protein (mg. %)	Glucose (mg. %)		
1	19·2	18·4	1·04	–	CG+	424	240	21	–	
2	38·2	27·6	1·38	+	G+	62	120	43	– (milk)	Tuberculous meningitis
3	27·0	27·0	1·00	+	C–	350	260	15	–	
4	30·8	25·9	1·19	+	C–G–	244	180	20	+	
5	20·2	18·4	1·10	+	C–	230			+	
6	24·2	28·1	0·86	+	C–G+	128	128	40	–	
7	33·0	17·2	1·92	–	C–G–	1,340	80	45	–	Non-specific meningitis
8	13·9	5·8	2·40	–	G–	176	30	49	–	Non-specific meningitis
9	13·8	4·75	2·90	–	C–	266	55	60	+	Poliomyelitis
10	28·3	13·2	2·18	+	C–	3	80	62	–	Tuberculoma of cerebellum
11	27·3 / 38·0	25·0 / 15·6	1·09 / 2·40	–	G–	260	150	55		Non-specific meningitis
12	45·0	13·5	3·35	–	C–	454	30	46	–	Non-specific meningitis
13	33·4 / 47·5	24·0 / 35·0	1·40 / 1·36	–	C–	828	30	40	–	Non-specific meningitis
14	42·0 / 48·0	24·5 / 26·3	1·72 / 1·82	–	C–	324	58	52	+	Mumps. Encephalitis
15	13·8	5·6	2·45	–	C–	62	40	90	+	Non-specific meningitis
16	14·9	7·2	2·05	–		800	48	55	–	Non-specific meningitis
17	37·3 / 59·4	19·4 / 30·6	1·93 / 1·93	+	C+ (from foot)	94	35	43	–	Miliary tuberculosis
18	14·2	5·7	2·50	–	C–	20	54	40	–	Mumps. Encephalitis
19	38·4	13·4	2·90	–	C–G–	432	30	37	–	Mumps. Encephalitis
20	23·8	8·6	2·76	–		90	70	70	+	Non-specific meningitis
21	30·4	15·2	2·00	–		3	32	78	–	Non-specific meningitis
22	25·0	11·4	2·20	+ (BCG)	C–	140	60	59	+	Poliomyelitis
23	27·5	12·3	2·24	–	C–G–	216	70	46	+	Non-specific meningitis
24	51·5	22·8	2·25	–	C–	202	40	67		Poliomyelitis
25	18·1	9·5	1·92	–		90	20	80	–	Mumps. Encephalitis
26	51·5	21·9	2·36	–	C–	48	35	54	+	Poliomyelitis

Material and Results

In the six cases of tuberculous meningitis (Table 2) the bromide ratio was depressed in all cases. In Cases 3 and 5 the test was useful in confirming the clinical diagnosis. Case 1 presented the typical features of tuberculous meningitis but the Mantoux reaction was negative on admission. A bromide ratio of 1·04 was useful additional evidence in favour of the diagnosis. Cases 2, 4 and 6 presented diagnostic problems as the clinical picture was not typical, and, as they illustrate the practical value of the test, they are presented more fully.

Case 2. A girl, aged 5 years, was well until the day of admission when she was suddenly unable to speak, did not recognize her mother and looked vacant for a few minutes. She vomited at the end of the attack. There was nothing relevant in her previous or family history, but the milk supply was from a doubtful source. The child was well on admission and physical examination was negative. Investigations included: haemoglobin 81%, white blood cells 8,000 per c.mm., 62% polymorphs. The urine was normal and there were no pathogens in the stool. A Mantoux test was 1:1,000 positive. Radiographs of the skull and chest were normal, while that of the abdomen showed calcified mesenteric glands. She was well for 10 days when she had a further minor convulsion lasting a few seconds. Three days later she was less well and vomited several times. Physical examination remained negative. Lumbar puncture showed 62 cells per c.mm., protein 120 mg. %, glucose 43 mg. %. She was thought possibly to be suffering from early tuberculous meningitis and was started on streptomycin, isoniazid and P.A.S. while a bromide partition test was done, the ratio being 1·38 which was in favour of the diagnosis. A guinea pig inoculated with the original cerebrospinal fluid showed evidence of tuberculosis. She made an excellent recovery.

Case 4. A boy, aged 2 years, whose father had recently been admitted to a sanatorium with pulmonary tuberculosis, was found to have an early primary complex just discernible on his contact film. Unfortunately, the family did not attend for their Chest Clinic appointment and shortly afterwards this child was admitted following a convulsion with a history of vomiting and irritability of one week's duration. On examination he was unconscious and twitching. There was no meningism, or localizing signs in the central nervous system. He had an acute right otitis media requiring paracentesis, otherwise physical examination was negative. Investigations included haemoglobin 68%, white blood cells 11,000 per c.mm., 50% polymorphs. A radiograph of the skull was normal, that of the chest showed a right primary complex. Pus from the right ear was sterile and *M. tuberculosis* was not isolated. Cerebrospinal fluid cells were 244 per c.mm., 91% lymphocytes, protein 180 mg. %, glucose 20 mg. %. A Mantoux test was 1:1,000 positive. The child was thought to be suffering from tuberculous meningitis and was started on treatment with streptomycin, isoniazid and P.A.S. A bromide ratio of 1·19 confirmed this diagnosis and was useful in ruling out the possibility that he was suffering from an intracranial complication of his ear disease.

Case 6. A girl, aged 6 years, was admitted as a 'pyrexia of unknown origin' with a five days' history of headache, abdominal pain and vomiting. Physical examination was negative. Routine investigations included haemoglobin 72%, white blood cells 14,000 per c.mm. A radiograph of the chest was normal. The urine contained a trace of albumen. Agglutinations to *Salmonella* and *Brucella* groups were negative. A blood culture was sterile and there were no pathogens in the stool. A Mantoux test was 1:1,000 positive. Cerebrospinal fluid cells were 128 per c.mm., protein 128 mg. %, glucose 40 mg. %. Bromide ratio 0·86.

During the investigations apart from a pyrexia she remained relatively well and there were no clinical signs of tuberculous meningitis until the diagnosis had been made and she was on treatment with streptomycin, isoniazid and P.A.S.

In the above six cases presenting as tuberculous meningitis, proof of the diagnosis was obtained in five. Three were confirmed by guinea pig inoculation (Cases 1, 2, 6) and two others developed choroidal tubercles (Cases 4, 5). In the remaining case the subsequent course of the disease was typical of tuberculous meningitis, and there is little doubt about the final diagnosis. Treatment with antituberculous drugs does not affect the bromide ratio in the early stages. Cases 1, 2, 4, 5 and 6 were started on treatment a few days before or during the bromide partition test. Case 3 had been on treatment for 17 days when the test was done. This is particularly useful as treatment may be started at once in uncertain cases without affecting the result, and, conversely, the patient need not be committed to a full course of treatment in the event of a negative result.

Case 14 illustrates the latter point. A child, aged 15 months, whose father had had a recent pulmonary tuberculosis, was admitted following a convulsion. Ten days previously his brother had developed mumps and he had had transient facial swelling. Physical examination was normal. Relevant investigations included a Mantoux test 1:1,000, and 100 negative. Radiographs of the chest and abdomen were normal. Cerebrospinal fluid cells were 324 per c.mm., 89% lymphocytes, protein 58 mg. %, glucose 52 mg. %. The fluid was taken on admission at night and a technician reported acid-fast bacilli in the smear. In view of this he was started on treatment with streptomycin, I.N.A.H. and P.A.S. The bromide ratio was 1·72 and a repeat ratio 1·82. In view of the history, clinical course and high bromide ratio he was thought to be probably suffering

from mumps encephalitis and he did not have a full course of anti-tuberculous drugs.

The bromide ratio is said to rise when infection is brought under control (Taylor, Smith and Hunter, 1954). In three of our cases repeat bromide partition tests were done during treatment (Fig. 2). Clinical improvement was accompanied by a rising ratio in each case. In Case 6 when the response to treatment was initially poor, the bromide ratio remained low, rising later when the clinical condition was also improving.

In the 20 cases of non-tuberculous meningitis the bromide ratio was normal in 18 of the cases. It was particularly helpful in six of these children (Cases 9, 15, 20, 22, 23, 26) who presented with early non-purulent meningitis and in whose case there was a family history of tuberculosis. Further, when poliomyelitis has been prevalent, or when there has been a history of contact with a disease such as mumps when encephalitis may occur, the bromide partition test has been a useful aid in eliminating tuberculous meningitis which must always come into the differential diagnosis.

Three of the cases with normal bromide ratios had positive Mantoux reactions. One had had B.C.G. The other two, one of interest, are presented more fully.

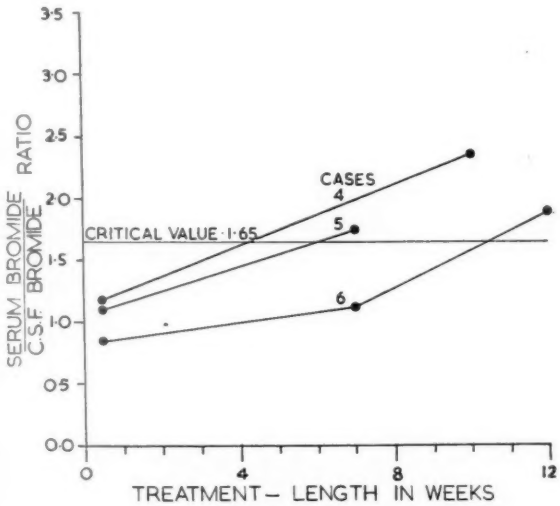


FIG. 2.—Alterations in the $\frac{\text{serum bromide}}{\text{C.S.F. bromide}}$ in tuberculous meningitis cases treated with P.A.S., I.N.A.H. and I.M. streptomycin.

Case 10. A girl, aged 9 years, was admitted with a history of general ill health, poor appetite, loss of weight and a noticeable falling off in her school work, of one year's duration. In the five days before admission she had had six attacks of headache, nausea and vomiting followed by unconsciousness for one minute. Physical examination was normal apart from a systolic murmur in her heart (pulse 86 per minute, blood pressure 95/50) and early papilloedema. Investigations included haemoglobin 78%, white blood cells 7,000 per c.mm., 74% polymorphs. The E.S.R. was 60 mm. in one hour. Blood urea was 38 mg. %. Blood chemistry was normal. There was a trace of albumen in the urine. Radiographs of the chest and abdomen were normal. A radiograph of the skull showed increased digital markings. Lumbar puncture showed fluid at increased pressure, cells 3 per c.mm. mononuclear, protein 80 mg. %, sugar 62 mg. %, Lange 5,554,310,000. The Wassermann reaction was negative, a Mantoux test positive. In view of her positive Mantoux, raised E.S.R. and changes in the cerebrospinal fluid, a bromide ratio was done, which at 2·18 was against a diagnosis of tuberculous meningitis.

She developed increasing papilloedema and ataxia and was transferred to a neuro-surgical unit where craniotomy was performed. A tuberculoma of the cerebellum was found and successfully removed. The normal bromide ratio in this case was both helpful and interesting.

Case 17. A girl, aged 2½ years, was admitted with a history of a minor injury to her right foot a few days previously: an indurated swelling had developed at the site of the injury. On the day of admission she vomited and had a series of generalized convulsions. On examination she was convulsed and neck stiffness was present. There was a fluctuant swelling on the dorsum of her right foot and her right knee was swollen. There were no other abnormal signs. Investigations included haemoglobin 71%, white blood count 11,300 per c.mm.. 80% polymorphs. There were no pathogens in the stool, A radiograph of the skull was normal, that of the chest showed increased shadowing at the right hilum. A Mantoux test was 1:1,000 positive. Urine protein was 700 mg. %, with two pus cells per high power field in uncentrifuged urine. Blood urea was 34 mg. %. An E.S.R. was 21 mm. in one hour. Cerebrospinal fluid cells were 94 per c.mm., 19% polymorphs, 81% lymphocytes, protein 35 mg. %, glucose 43 mg. %. Pus from the swelling of the foot contained tubercle bacilli. The bromide ratio was 1·93.

She was thought to be suffering from miliary tuberculosis and was started on treatment with streptomycin, isoniazid and P.A.S.

The normal bromide ratio, which was confirmed on a repeat test, is interesting. Cheek (1956) quotes Taylor, Smith and Hunter as saying that in miliary tuberculosis not involving the central nervous system the bromide ratio remains normal. In this case the meningeal signs and cerebrospinal fluid changes occurred during the period of invasion and she did not develop a true tuberculous meningitis.

In two of the cases the bromide ratio was low, giving false positive results.

Case 11. A girl, aged 11 years, was admitted as a surgical emergency with abdominal pain which rapidly improved, but she developed a pyrexia and persistent

headache. Relevant investigations included a Mantoux test, 1:1,000 negative. Cerebrospinal fluid cells were 260 per c.mm., 94% lymphocytes, protein 150 mg. %, glucose 55 mg. %. She was kept under observation and put on no treatment while a bromide ratio was done, the ratio being 1·09. By then she was quite well and the cerebrospinal fluid was returning to normal. A repeat ratio was 2·40.

Case 13. A boy, aged 4 months, who had had signs of a cerebral injury in the neonatal period was admitted following a convulsion. Physical examination was normal. Relevant investigations included a Mantoux test, 1:1,000 negative. Cerebrospinal fluid cells were 828 per c.mm., 94% lymphocytes, protein 30 mg. %, glucose 40 mg. %. The bromide ratio was 1·40. The child remained well and, as the cerebrospinal fluid was also improving, he was given no treatment and continued to improve. A repeat ratio was 1·36. He made an uneventful recovery.

These results agree with those of Taylor, Smith and Hunter (1954) who reported 7% false positive results in their series.

Summary

The serum/cerebrospinal fluid bromide ratio ('bromide partition test') of Taylor, Smith and Hunter (1954) has been applied in 26 cases of non-purulent meningitis of which six were tuberculous and 20 non-tuberculous.

In the tuberculous cases the accuracy was 100%, no false negatives being obtained. In three of the tuberculous cases, the ratio was determined at intervals during treatment and clinical improvement was accompanied by a rising ratio.

In the non-tuberculous cases, the accuracy was 90%, two out of 20 cases giving false positive results (Cases 11 and 13). Similar findings have been reported by Taylor, Smith and Hunter who found a low ratio in 7% of 66 cases of non-tuberculous meningitis.

Taken in conjunction with the clinical findings, the bromide partition test appears to be a valuable adjunct in the early diagnosis of tuberculous meningitis and may prove also to be a useful criterion for following the course of clinical improvement.

We are grateful to Dr. P. Kidd for first drawing our attention to this diagnostic technique and to Dr. A. G. V. Aldridge for his interest in the work and for permission to publish material relating to his cases. Mr. F. Hughes kindly prepared Figs. 1 and 2 for us.

References

Cheek, D. B. (1956). *Pediatrics*, **18**, 218.
Hunter, G. (1953). *Biochem. J.*, **54**, 42.
——, Smith, H. V. and Taylor, L. M. (1954). *Ibid.*, **56**, 588.
Taylor, L. M., Smith, H. V. and Hunter, G. (1954). *Lancet*, **1**, 700.

PNEUMATOSIS INTESTINALIS IN CHINESE CHILDREN

BY

C. S. MUIR

From the Department of Pathology, University of Malaya

(RECEIVED FOR PUBLICATION MARCH 5, 1958)

Pneumatosis cystoides intestinorum hominis is a rare condition. Although about 250 cases have been described to date only seven of these have come from the Orient: five Chinese adults (Tung and Ngai, 1933; Yin, 1937; Ling, Ku and Su, 1948), and two Indian adults (Tribedi, 1941; Davies, 1941). This paper records five cases occurring in Singapore, one in an adult, the remainder in children.

The lesion consists of gas-containing cysts of varying size, either sessile or pedunculated, within the wall of the intestinal tract. There may, in addition, be similar cysts on the surface of other abdominal organs and on the parietal peritoneum.

Case Histories

Case 1. C.J.M., a 3-month-old male Cantonese child, was admitted to the General Hospital, Singapore, on August 20, 1953, and died five minutes after reaching the ward. The child's mother stated that he had had diarrhoea for the past two days. Over a similar period of time she had noticed increasing breathlessness. The child's temperature was 104° F. Dyspnoea was extreme and numerous crepitations were heard on auscultation of the lung bases.

Dr. E. B. La'Brooy, who performed an autopsy, reported that the body was that of a thin, male Chinese infant, height 2 ft. 4 in., weight 1 st. 1 lb. The heart appeared normal. The respiratory passages were partially blocked by mucopurulent exudate, and the lungs showed patchy areas of consolidation with areas of collapse posteriorly. The liver showed gross fatty change. Hyperaemia of the mucosa was present in the small intestine. Two lymph follicles showed superficial necrosis and bile staining of sloughing tissue. The large intestine showed several irregular ulcers of lymph follicles. There were numerous bubbles of gas in the mucosa of the ileum. The stools were not cultured.

HISTOLOGY. A section of colon showed well-marked pneumatosis. The majority of gas spaces had no lining endothelium (Fig. 1, top left). Several of these unlined spaces had giant cells in the wall and an occasional macrophage round about. Another space showed an incipient lining, which appeared to be formed by condensation of surrounding tissue. In this wall (Fig. 2), three giant cells were seen (cf. Fig. 30: Wright, 1930). Moderate numbers of macrophages were present in the neighbourhood.

Case 2. A.B.H., aged 1 month, a male Chinese infant, was admitted to the General Hospital, Singapore, in a dehydrated condition, with a three-day history of diarrhoea and vomiting after feeds. No pathogenic organisms were grown from the stools. The child died.

Dr. Ng Chiau Gian found a patent foramen ovale on autopsy. There was a thin layer of sero-purulent fluid inside the peritoneal cavity, and small mucosal ulcers in the lower part of the ileum and colon. In a portion of the ileal wall, which showed no signs of inflammation, there were numerous blebs of gas, possibly post-mortem in origin.

HISTOLOGY. Sections of colon showed a very well-developed pneumatosis. The gas spaces were lined by a low endothelium. Towards the centre of the section an abscess containing mononuclears, polymorphs and much debris was present. This extended from the mucosa to the muscle layers and was of the 'collar-stud' type (Fig. 3). Just below this abscess, within the muscle layers, an amoeba was seen (Fig. 4).

Case 3. G.H.J., a 1-month-old male Hokkien child, was admitted to the General Hospital, Singapore, on December 1, 1956, with a complaint of persistent regurgitation of feeds of several days' duration. A diagnosis of duodenal stenosis was made and on December 15 laparotomy was performed. A volvulus of mid-ileum was reduced and numerous adhesions divided. The child died on January 2, 1957, after a short period of vomiting.

At autopsy the body was that of a thin, male Chinese infant. The abdomen was rather bloated, and there was a well-healed transverse lower abdominal surgical scar. The heart appeared normal. The lung parenchyma showed early bronchopneumonic change. The normal anatomy of the gut was deranged by multiple adhesions: a major portion of caecum was tacked down to the liver and the appendix was adherent to the small bowel. The loops of small bowel were adherent to each other, showing numerous kinks although no definite obstruction

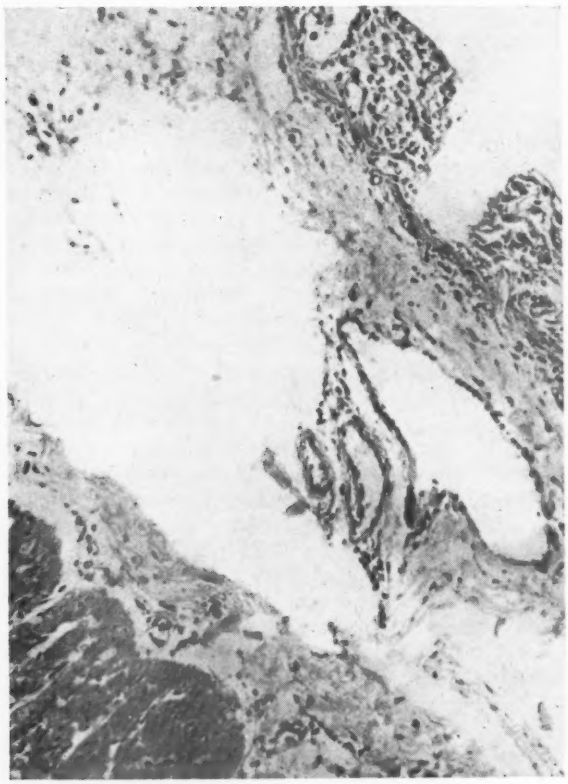


FIG. 1.—P.M. 1492/53. Section of intestinal wall showing, at middle right, a gas space with an incipient lining. On either side is unlined gas space. H. and E. × 135.

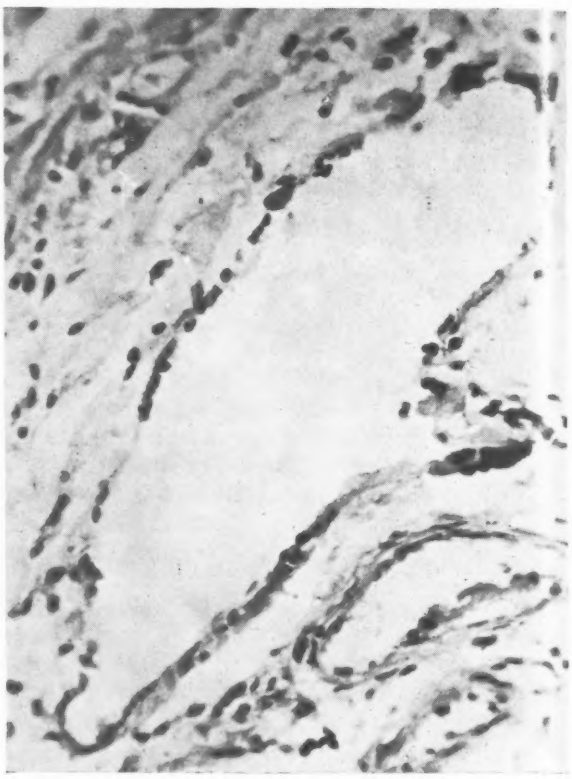


FIG. 2.—P.M. 1492/53. Higher magnification of the gas space above shows it to be partially lined by a condensation of surrounding tissue. In the wall three giant cells are seen. Moderate numbers of macrophages are present in the surrounding tissue. H. and E. × 336.

could be detected. One portion of jejunum was tacked down between the liver and the diaphragm. The gut was generally dilated, red in colour and in places showed desquamation of the mucosal epithelium.

HISTOLOGY. Section of the ileum showed pneumatosis (Figs. 5, 6 and 7). Nearly all the gas spaces had an endothelial lining although this was not well marked in places. Macrophages were moderately plentiful; the cytoplasm was less bulky than in other sections. Moderate numbers of giant cells were seen (Fig. 8).

Case 4. O.B.C., a 63-year-old Henghwa male, was admitted to the General Hospital, Singapore, on April 25, 1957, with a complaint of four months' increasing abdominal swelling. A firm nodular mass was palpated in the upper abdomen and the liver was grossly enlarged. He was considered to be suffering from gastric carcinoma.

Dr. A. O. Aaron's autopsy report stated that the heart appeared to be normal. The lungs were the seat of numerous small circumscribed tumour nodules. The liver weighed 4,300 g., being largely replaced by secondary tumour. There was no evidence of cirrhosis. There was a large circular carcinomatous ulcer 5 cm. in diameter on the lesser curvature of the stomach close to the pylorus. The submucosa of the ileum and colon showed pneumatosis.

HISTOLOGY. Section of the colon showed moderately well-developed pneumatosis. All the gas spaces were lined by a low endothelium. Very few giant cells or macrophages were seen.

Case 5. N.P.M., a 12-year-old Hokkien girl, was admitted to the General Hospital, Singapore, on December 26, 1957, and died one hour later. She gave a history of two days' abdominal pain associated with vomiting. She had passed numerous stools on the day prior to admission.

At autopsy the heart appeared normal. The lungs showed changes, possibly early bronchopneumonic. The entire gut from mid-jejunum to descending colon was inflamed and showed areas of patchy superficial necrosis. The necrotic areas were deeply bile stained. In the mid-jejunum and upper ileum several small areas, each about 5 cm. long, were seen which showed air bubbles in the gut wall. This was probably early pneumatosis.

HISTOLOGY. Section of the lower jejunum (Fig. 9), showed a moderate degree of disruption of the tissues of the sub-mucosa. This was presumably caused by gas. Around these areas macrophages and eosinophils were prominent (Figs. 10 and 11; cf. Fig. 25: Wright, 1930). These macrophages had a prominent ovaloid nucleus and a bulky homogeneous pink cytoplasm.

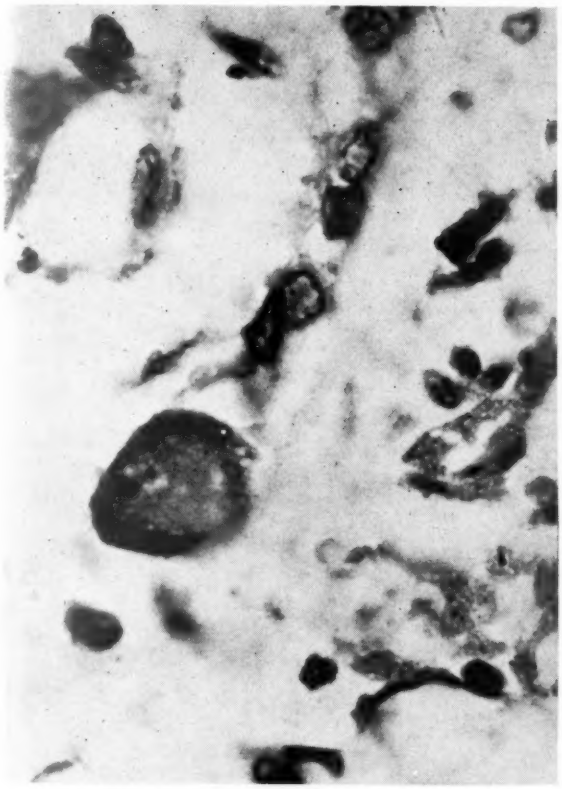


FIG. 3.—P.M. 1167/57. Amoebic abscess of ascending colon superimposed on pneumatosis. H. and E. × 135.

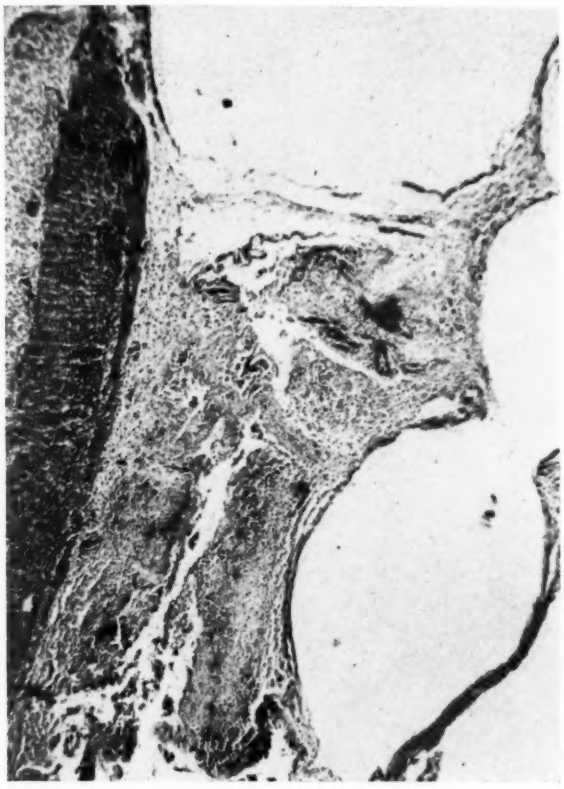


FIG. 4.—P.M. 1167/57. An amoeba within the muscle coats. H. and E. × 1,200.

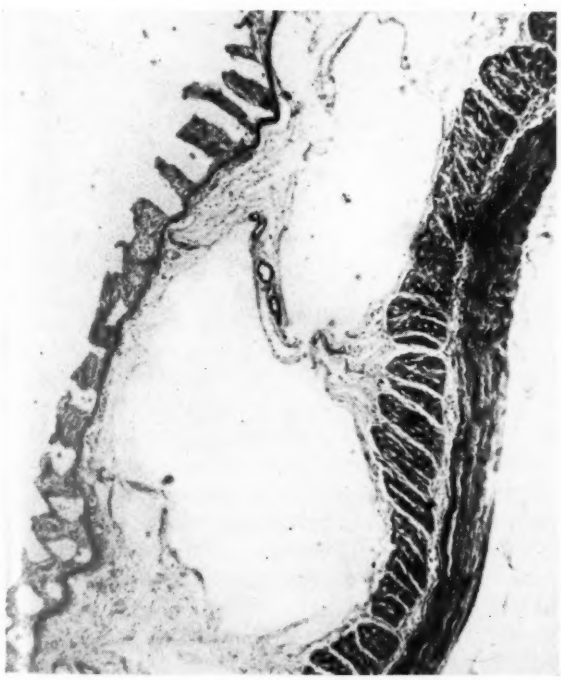


FIG. 5.—P.M. 7/57. Section showing submucosal pneumatosis.

Elsewhere in the section several lined gas spaces were seen. One of these (Fig. 12), was lined for about three-quarters of its circumference by a low endothelium, the remainder by a condensation of surrounding tissue. Around this space moderate numbers of macrophages were present.

Aetiology

The exact cause of pneumatosis is unknown. Several theories have each, from time to time, attracted some support.

First in the field was the neoplastic hypothesis. Bang (1876) described the first well-documented case and considered the cysts to be the product of a new growth, which, taking its origin from giant cells in the lymphatic vessels, spread, elaborating a gas as it did so. Mair (1907) believed that the lesion was a true neoplasm whose cells produced gas. Finney (1908) who reported the first American case subscribed to this viewpoint.

The bacterial theory attracted workers who considered that the cysts were the work of gas-producing organisms. Dupraz (1897) did, indeed, isolate a variety of organisms which he termed *Bacterium*

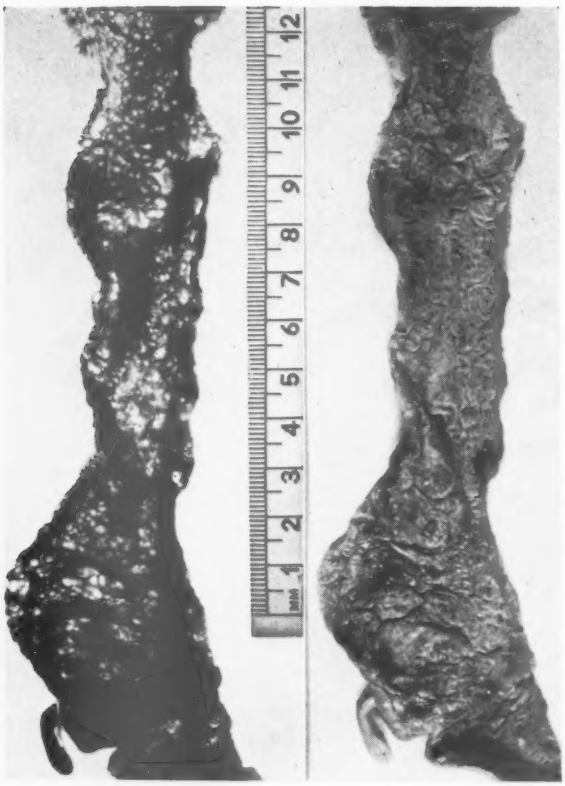
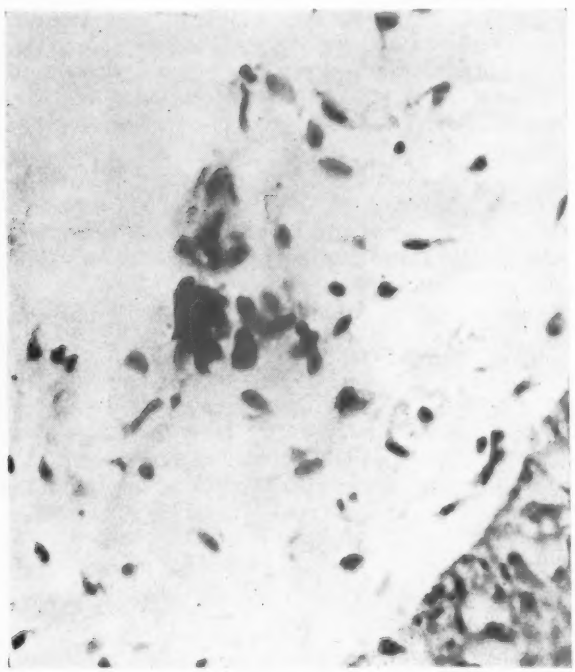


FIG. 6.—P.M. 7/57. Macroscopic appearance of caecum by incident light.

FIG. 7.—Same portion of gut as in Fig. 6. By transmitted light the extent of involvement is much more readily appreciated.



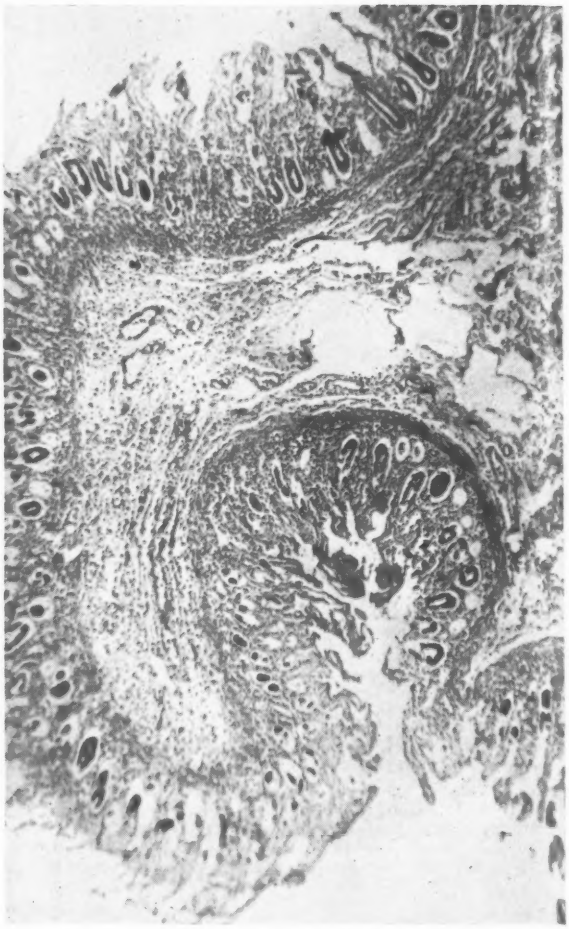


FIG. 9.—P.M. 2609/57. The lower jejunum shows a moderate degree of disruption of the sub-mucosal tissues. H. and E. × 37.

coli lymphaticum aerogenes which, if given orally to animals, reproduced the lesions. All his animals died, however, within 48 hours. Naeslund (1924) cultured from gas cysts in the intestinal wall of swine a variant of *Esch. coli* which he termed *Bacillus pneumatosis*. He obtained weakly positive serological reactions between a suspension of these organisms and the sera of positive swine. Healthy animals, i.e., those without gas cysts of the intestines, did not show this reaction. Injection of these bacteria failed to reproduce the lesions.

The biochemical theory is favoured by those who draw an analogy between the lesions in man and those occurring in the pig. Swine suffer from the condition quite frequently, a fact known since Mayer (1825) described the condition in an otherwise healthy hog. Known as swine emphysema it is

FIG. 8.—P.M. 7/57. A giant cell in the wall of a partially lined gas space. H. and E. × 336.

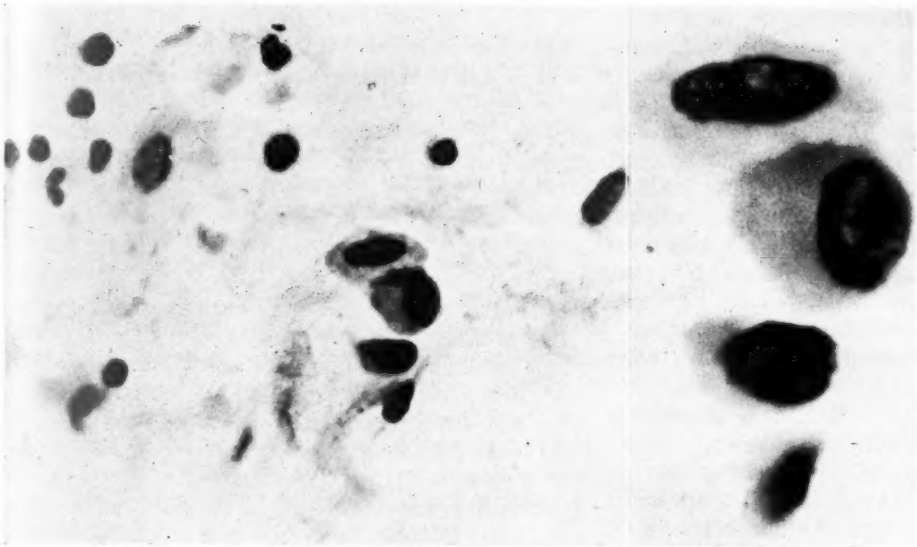


FIG. 10.—P.M. 2609/57. Macrophages around the gas spaces in the intestinal wall. H. and E. × 880.

FIG. 11.—P.M. 2609/57. The macrophages in Fig. 10 at a higher magnification. H. and E. × 2,200.

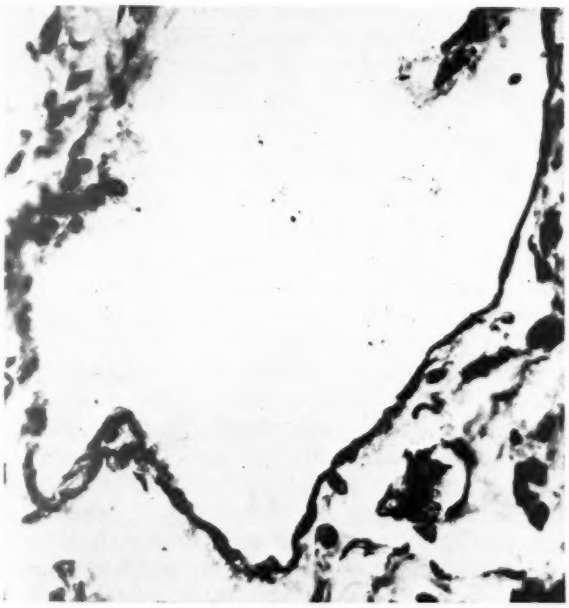


FIG. 12.—P.M. 2609/57. A low endothelium partially lines this gas space on the bottom and right sides, blending gradually at the top left into a condensation of the surrounding tissues. Moderate numbers of macrophages are present. H. and E. × 350.

related in some way to diet, as the disease can be readily reproduced on feeding a diet of polished rice (Biester, Eveleth and Yamoshiro, 1936). Such a relationship is not apparent in man. Pneumatosis has also been observed in sheep (Mills, 1925) and in chickens (Naeslund, 1924).

At present the mechanical theory seems to attract the most adherents. If air be injected directly into the gut wall it follows the lymphatics to the mesentery and within a few days is gradually absorbed. Masson (1925) concluded that lymph stagnation is the basis of the phenomenon. This occurs in tortuous or obstructed lymph vessels, carbon dioxide and lactic acid being absorbed into the obstructed segment. Carbon dioxide is liberated and nitrogen, oxygen and methane diffuse in, the relative proportions of the gases being governed by their partial pressures.

Tung and Ngai (1933) expended considerable effort in trying to reproduce pneumatosis in the dog. They attempted to mimic as closely as possible the conditions obtaining in their patients, both of whom had, in addition to pneumatosis, stenosing peptic ulcers. They reproduced such a stenosing ulcer in one of their dogs and filled the stomach with air and salt solution. Air bubbles appeared, both inside and outside the lymphatics, which moved distally with each peristaltic movement. The animals were allowed to recover from anaesthesia. On the second day after operation the dogs vomited, refused to eat, and appeared quite sick. On reopening the abdomen air bubbles were seen in the lymphatics of the gastric serosa and in those of the omental attachments. Straus (1954) attempted to do the same in the large intestine of the dog. He found that gas cysts did form slowly if air were injected into the lumen of a segment of bowel which had been obstructed both distally and proximally. It seems, therefore, that obstruction favours the formation of these cysts, although it cannot be the whole answer as one would expect to see them more frequently in association with, say, obstructing carcinomata of the colon.

Pathology

The ileum, followed by the colon, are the most frequently affected portions of the gut; both may be involved at once (MacKenzie, 1951). The stomach and gall bladder (Mills, 1925) and the falciform ligament of the liver (Pybus, 1934) have been reported as affected. The amount of gut involved varies. It is often confined to a loop constricted by adhesions or volvulus, sometimes to a loop containing intestinal parasites, usually nematodes (Tung and Ngai, 1933). In the adult the gas cysts are found mainly in the serosa. In children the cysts tend to be submucosal, cysts in the muscle coats being rare. The average cyst is 4-5 mm. in diameter. Koss (1952) reports one cyst 3·5 cm. in diameter in the distal caecum. The gas is a mixture of 70-90% nitrogen, 3-20% oxygen, and 0-15% carbon dioxide. Traces of methane have been detected (Urban, 1910).

In children the cysts appear microscopically as thin-walled sacs lined entirely, or in part, by a single layer of flat endothelium. This lining may not be present. In adults as a rule giant cells are present; in the child they may not be so conspicuous. Wright (1930) has shown that air acts as a foreign body evoking a giant cell response. These giant cells are in many instances mere aggregations of nuclei some 10 to 50 in number and are found near the gas-filled space (Fig. 8). Tung and Ngai (1933) describe in their adult cases a second type of cyst lined by a dense fibrous tissue. In their Fig. 6 they show giant cells in the lumen of one example of this type of cyst, which they regard as being older than the thin-walled variety. They made serial sections of their specimens and found that the endothelium lined spaces communicated with lymphatic vessels, whereas the fibrous variety did not. Koss (1952), examining serial sections, was unable to demonstrate a breach of the continuity of mucosa in the region affected by gas cysts or to demonstrate a definite transition between a cyst and a lymphatic vessel. It seems, therefore, that in time the thin-walled cysts become fibrosed and obliterated. The photomicrographs in his paper show a similar disposition of the giant cells in thick-walled cysts.

Clinical Features

In the infant the most common presenting symptom is diarrhoea (Botsford and Krakower, 1938; Judge, Cassidy and Rice, 1949; MacKenzie, 1951). In the adult pyloric obstruction following peptic ulcer is found in about 60% of cases (Nitch and Shattock, 1919). Pyloric lesions tend to be associated with pneumatosis of the small gut, while obstructive signs are found more commonly with large gut lesions (Kreeger and Littmann, 1954).

Intestinal obstruction is, particularly in the adult, the most likely complication. This may be precipitated by volvulus induced by the cyst mass, by the adhesions which seem to arise as a result of the cysts, or by mechanical blockage of the bowel lumen. Koss (1952) quotes a case in which pneumatosis caused intussusception. Haemorrhage from the bowel may occur (Matthews, 1954; Kreeger and Littmann, 1954; Pontius, 1954). Pneumoperitoneum will result if a sufficient number of cysts burst.

Diagnosis. Diagnosis is usually made on the operating table or at autopsy.

A straight radiograph of the abdomen may be helpful, particularly so if there should be a pneumoperitoneum. Pneumoperitoneum may be simulated by the gas from the mesenteric cysts passing retroperitoneally and accumulating between the parietal peritoneum and the diaphragm. The so-called Chilaiditi sign (the interposition of a loop of bowel between liver and diaphragm) is often positive. Barium meal or enema will show filling defects. The condition has been diagnosed on sigmoidoscopy (Matthews, 1954) and on sigmoidoscopic biopsy (Kreeger and Littmann, 1954).

Treatment. Incidental discovery calls for no active measure. Koss (1952) has observed that the disease is self-limiting. Should obstruction occur the offending segment of gut may be removed. There appears to be no agreement as to how the lesion should be treated in childhood.

Discussion

Apart from the submucosal situation of the cysts, Case 4 is typical of pneumatosis in the adult. The rest show features common to nearly all others described in infants. Diarrhoea was the presenting symptom. A volvulus with intestinal obstruction and adhesions were found in Case 3. This latter case shows the Chilaiditi sign, a not infrequent occurrence in pneumatosis with small bowel involvement. Koss (1952) would exclude many of the cases reported in children, preferring to class them as intestinal emphysema. He observes that in many of these cases on microscopy, the cyst wall is devoid of epithelial lining, and cites the cases of Botsford and Krakower (1938) and Judge *et al.* (1949). He states, 'The cases in which there is evidence of cyst lining are accepted, and the others are considered as cases of emphysema, possibly a terminal event, with intestinal gas penetrating into the intestinal wall generally and not selectively into the lymphatics.'

While one must respect the views of the author of a careful and exhaustive review, he and many

others have failed to appreciate the significance of the work of Wright (1930). Wright injected, under aseptic conditions, various gases into the subcutaneous tissues of guinea pigs. He found that nitrogen remained in the tissues for three days after injection and at the end of this time the crepitation typical of surgical emphysema could still be elicited. With oxygen, a gas which diffuses much more readily, crepitation could be detected at the end of 24 hours.

A study of the cellular response to these gases showed that while the response varied quantitatively with each gas used, qualitatively it was much the same. Within two days of the introduction of gas into the subcutaneous tissues, tissues which are surely not so different from those of the sub-mucosa or sub-serosa, there appeared round the gas spaces epithelioid type cells, derived, he felt, from the monocytes, by virtue of their appearance when stained supravitally. By the tenth day numerous giant cells derived from these epithelioid-like cells were present, some being 15-40μ in diameter. By the fourth day portions of the walls of the gas spaces were lined by flat cells, which morphologically resembled an endothelioid or serous lining. Although he thought that the possibility that these cells arose from capillary or lymphatic endothelium could not be ruled out, he could find no evidence that they did so and concluded that this lining arose from the epithelioid cells. By the end of two months the walls of these gas spaces were thickened and the lumina contained many giant cells, a picture closely resembling the 'older' cysts of Tung and Ngai (1933).

Although the author has been unable to identify the epithelioid nature of the cells described by Wright (1930), nearly all the sections examined from the cases of pneumatosis described showed a characteristic cell which has been described as a macrophage in the text. This cell, with an oval or round nucleus and a homogeneous dusky pink cytoplasm, is found in great numbers around early lesions and to a lesser extent around the more advanced ones. This cell may be the intestinal counterpart of Wright's epithelioid cell, and, indeed, cells which are described as mononuclears in Fig. 25 of his paper look identical with the author's macrophages.

The sequence of events would thus seem to be:

(*a*) The intestinal gases gain entrance to the sub-mucosal tissues, disrupting them to form gas spaces (Fig. 9) around which a macrophage response is evoked (Fig. 10).

(*b*) The tissues surrounding these spaces condense to form a lining, which gradually becomes altered to an endothelium (Figs. 2 and 12). In these walls typical giant cells, probably derived from the macrophages, are found (Figs. 2 and 8).

(*c*) As the gas space, now a lined gas cyst, becomes older, it may either dilate as in Figs. 5 and 6 or sclerose as in the cases of Tung and Ngai (1933).

This histological interpretation is open to criticism. It does not explain the mode of formation of sub-serosal gas cysts, nor the mode of entry of the gases when there is apparently no breach in the gut wall. It may be that there are two mechanisms of genesis for pneumatosis, a lymphatic one, and the more mechanical one outlined above. It is felt that the exclusion of certain cases by Koss (1952) is, on the basis of the evidence presented above, unwarranted. The immunological approach of Naeslund (1924) is worth repeating.

It is not without interest to note that even in the fresh specimen I could not elicit the crepitation which is so characteristic of subcutaneous emphysema. Although this absence of crepitus has not been commented on before, no reference to its presence could be found in other cases.

Summary

Five cases of pneumatosis occurring in persons of Chinese race are reported. The literature is briefly reviewed. Special reference is made to the differences of opinion which exist on the classification of gas cysts of the intestine in children, and a theory of pathogenesis for the condition is promulgated.

I wish to thank Professor Kirk for kind help and criticism; Mr. V. Nalpon for sections and photomicrographs and my wife for secretarial assistance.

References

Bang, B. L. F. (1876). *Nord. med. Ark.*, **8**, 1. (Cited by Finney (1908). *Loc. cit.*)
Biester, H. E., Eveleth, D. F. and Yamashiro, Y. (1936). *J. Amer. vet. med. Ass.*, **88**, 714.
Botsford, T. W. and Krakower, C. (1938). *J. Pediat.*, **13**, 185.
Davies, S. T. (1941). *Indian med. Gaz.*, **76**, 94.
Dupraz, A. L. (1897). *Arch. Méd. exp.*, **9**, 282.
Finney, J. M. T. (1908). *J. Amer. med. Ass.*, **51**, 1291.
Judge, D. J., Cassidy, J. E. and Rice, E. C. (1949). *Arch. Path. (Chicago)*, **48**, 206.
Koss, L. G. (1952). *A.M.A. Arch. Path.*, **53**, 523.
Kreeger, N. and Littman, L. (1954). *New Engl. J. Med.*, **251**, 779.
Ling, C. Y.. Koo, S. N. and Su, Y. H. (1948). *Chin. med. J.*, **66**, 435.
MacKenzie, E. P. (1951). *Pediatrics*, **7**, 537.
Mair, W. (1908). *Med. Chron.*, **47**, 422.
Masson, P. (1925). *Ann. Anat. path.*, **2**, 541.
Matthews, F. J. C. (1954). *Brit. med. J.*, **1**, 851.
Mayer, J. (1825). Quoted by Koss (1952). *Loc. cit.*
Mills, H. W. (1925). *Surg. Gynec. Obstet.*, **40**, 387.
Naeslund, J. (1924). Zur Kenntnis der Pneumotosis cystoides intestinorum. Thesis. Uppsala, Stockholm.
Nitch, C. A. R. and Shattock, S. G. (1919). *Proc. roy. Soc. Med.*, Sect. of Path., **12**, 46.
Olson, J. D. (1954). *A.M.A. Arch. Surg.*, **68**, 899.
Pontius, G. V. (1954). In discussion on paper by Olson (1954). *Loc. cit.*
Pybus, F. C. (1934). *Brit. J. Surg.*, **21**, 539.
Straus, F. H. (1954). In discussion on paper by Olson (1954). *Loc. cit.*
Tribedi, B. P. (1941). *Calcutta med. J.*, **38**, 285.
Tung, P. C. and Ngai, S. K. (1933). *Chinese med. J.*, **47**, 1.
Urban, K. (1910). *Wein. med. Wschr.*, **60**, 1750.
Wright, A. W. (1930). *Amer. J. Path.*, **6**, 87.
Yin, Y. C. (1937). *Chinese med. J.*, **51**, 541.

PHYSICAL DEVELOPMENT OF SCHOOLGIRLS IN UPPER BURMA

BY

C. V. FOLL

From the Burma Oil Company (1954) Ltd., Rangoon

(RECEIVED FOR PUBLICATION MARCH 17, 1958)

It is still popularly believed that the onset of menstruation occurs earlier in tropical climates than in temperate ones. Ellis (1950) studied puberty in Nigeria and found, in his second series, that the median age of the menarche was 14·4 years. This was significantly later than Wilson and Sutherland's (1949) figure of 13·6 for Oxford schoolgirls, the same authors' (1950) figure of 13·49 for Dorset, Oxford and Essex schoolgirls, and Provis and Ellis's (1955) figure of 13·35 for Edinburgh schoolgirls. Wilson and Sutherland (1950) also recorded some observations from Ceylon, and showed a distinct urban-rural difference in the mean age of the menarche; the respective ages being 12·84 and 14·39 years. Such urban-rural differences were not found in their English series.

In this paper it is hoped to confirm Ellis's Nigerian findings and also to provide some information about schoolgirl growth and development in Burma.

Social Factors, Nutrition and Environment

During December, 1957, 702 schoolgirls, aged 10 to 18 years, were interviewed in Chauk, a town of some 25,000 inhabitants in Upper Burma. The girls were predominantly Burmese, the remaining few being Chinese, Indian or Anglo-Indian. Chauk is a relatively wealthy town and food is plentiful, the basic diet being vegetable (occasionally meat) curry and rice. Some fish and fresh vegetables would commonly be included in most diets. Malnutrition is rarely seen in the town.

Chauk is about 1,470 miles north of the Equator, and in the hot weather the temperature reaches about 112° F. There are approximately 24 inches of rain each year. There is no malaria and the 'dry zone' in which it lies is one of the healthiest parts of Burma.

The schoolgirls were asked their age and whether or not they had started menstruating. Unlike many tropical peoples where age estimation is largely guess-work, the Burman has an accurate knowledge of his children's ages for several reasons. It is customary for almost all Burmans to have a horoscope made; this is based on an absolutely accurate time and date of birth. Many important decisions are made only after consulting the horoscope, and propitious days are sought for weddings, going into hospital for operations or deliveries, opening new cinemas and other business undertakings. A Burmese year consists of 12 lunar months, alternately 29 days and 30 days long. During the course of every third year there is an extra month. Each full moon is treated as a Sabbath day and many are times of special celebration.

The schoolgirls' heights and weights were also recorded. Weighing was done with the girls clad in angyis (nylon or cotton blouses) and longyis (type of long, usually cotton, skirt). The total weight of clothes would be less than 2 lb. Their height was recorded with the girls barefooted.

Age of Menarche

From the results obtained, it was possible to calculate graphically by probit analysis the 'median' age of the menarche, that age at which half the girls have started their periods; this was found to be 14·4 years. Table 1 shows a comparison between this figure and those obtained by Ellis (1950) and by Wilson and Sutherland (1950).

TABLE 1

COMPARATIVE AGE OF MENARCHE IN VARIOUS GROUPS

Series		Median Age of Menarche
Wilson and Sutherland (England)	(1949)	13·6
	(1950)	13·6
Ellis and Provis (Scotland)	(1955)	13·35
Ellis (Nigeria)	(1950) 1st series	14·22
	2nd ,,	14·40
Wilson and Sutherland (Ceylon)	(1950) Urban	12·10
	Rural	14·5
This Series (Burma)	(1957)	14·40

From the table it may be seen that the Chauk results confirm Ellis's findings in Nigeria, and also Wilson and Sutherland's rural results in Ceylon.

Height and Weight

Table 2 shows the mean heights and weights arranged in age groups before and after the menarche.

TABLE 2

NUMBERS, MEAN HEIGHTS AND WEIGHTS OF CHILDREN IN PRESENT SERIES

Age	Before Menarche			After Menarche		
	No.	Height (in.)	Weight (lb.)	No.	Height (in.)	Weight (lb.)
10	72	48·37	53·85			
11	91	49·97	57·22	1*	53·00	84·00
12	85	52·48	66·09	8*	57·56	77·88
13	58	53·65	73·26	49	54·83	84·43
14	20	55·50	82·50	71	55·46	88·07
15	3*	56·50	84·00	100	55·24	91·33
16	1*	54·00	82·00	74	55·36	93·86
17	2*	54·30	88·00	47	54·23	93·59
18				20	54·88	90·70

* Numbers too small to be of significance.

It may be seen that there is considerable increase in height from year to year until the age of 14 is reached, after which height remains almost constant. There is a similar increase in weight. The cessation of growth in height at the age of 14 is earlier than in the English series and it appears from these results that growth may take place earlier in children in the tropics. For instance, the average height and weight for a Scottish girl aged 11½ years (Provis and Ellis, 1955) is 55·7 in. and 74·5 lb. (nude weight). In this series, for a Burman 11½ years old, the height was 50 in. and weight 57 lb., a difference of 5·7 in. and 17·5 lb. This is considerably less than differences in height and weight of the older children as will be shown later.

Another factor that must be considered is that there is a substantial drop in the heights of the 17-year-old group, i.e. those girls born in 1940-41. These children would have suffered during their infancy from the various privations that were common during the Japanese invasion and occupation. A further series taken in 5 years' time would no doubt throw further light on this. Generally speaking children stay at school until older in Burma than in England.

The height difference between the pre-menarche group aged 13 and 14 is 1·85 in.; this group is largely composed of girls who will start menstruating the following year. This pre-menarchial growth spurt has been reported on by Simmons and Greulich (1943).

Comparison between 13- and 14-year-olds before and after the menarche shows a very slight difference in height but a marked difference in weight. This might be taken to confirm the view of Wilson and Sutherland (1950) that increase in height at this age is unaffected by sexual development, though it could also mean that the pre-menarchial spurt of growth has already occurred by the age of 14.

Body Build

The measure used is the height (in inches) divided by the cube root of the weight (in pounds); the means of height and weight for each group were used (Table 3).

TABLE 3

BODY-BUILD (MEAN HEIGHT IN IN. DIVIDED BY CUBE ROOT OF MEAN WEIGHT IN LB.)

Age	Body-build	
	Before Menarche	After Menarche
10	12·80	
11	12·96	*
12	12·98	*
13	12·82	12·49
14	12·75	12·47
15	*	12·21
16	*	12·18
17	*	11·94
18		12·21

* Fewer than 10 measurements, value omitted.

In the pre-menarche group it may be seen that height and weight increase in the same proportions. but the post-menarche group shows that girls become heavier for their height.

This study also shows that the Burmese girl is considerably smaller than her English counterpart. For instance the average weight and height (from Wilson and Sutherland's, 1950, series) of a 13½-year-old English girl who has not menstruated is 95·8 lb. and 60·8 in.; her Burmese contemporary weighs 73·3 lb. and is 53·6 in. tall. Similarly the English figures for a post-menarche 14½-year-old are 119·9 lb. and 62·5 in. compared with the Burmese 88·1 lb. and 55·5 in. In other words, the Burmese girl of 13-14 years onwards is some 7 in. shorter and 20-30 lb. lighter than the English girl. That they are smaller from birth has been reported on in an earlier study in Chauk, where the average birth weight for some 200 consecutive single deliveries in 1957 was found to be 6 lb. 7 oz. for boys and 6 lb. 3 oz. for girls (Foll, in press).

The average figures for Scottish newborns (full term by dates, but not all weighing more than 5½ lb.) were 7 lb. 9 oz. (boys) and 7 lb. 5 oz. (girls).

Summary

A study has been made of 702 predominantly Burmese schoolgirls in Chauk, Upper Burma.

The median age of the menarche is found to be 14·4 years, thus confirming Ellis's (1950) view that the onset of menstruation takes place later in tropical climates and not earlier as is often believed.

The study of height and weight confirms Wilson and Sutherland's (1950) suggestion that in adolescent girls growth is of two superimposed types: physical growth dependent on age and sexual growth dependent on sexual development.

It is suggested that growth starts earlier in the tropics and that little growth in height takes place after the age of 14.

Early nutritional deprivation may well have an effect on subsequent growth.

The Burmese girl is shown to be lighter and shorter than her English and Scottish contemporary.

I am indebted to Professor R. W. B. Ellis for his advice and helpful criticism in the preparation of this paper; also to the Management of the Burma Oil Co. (1954) Ltd. for facilities granted to me, to the headmasters of the various schools who so willingly co-operated, and especially to Dr. Onmar Khin who interviewed the children.

REFERENCES

Ellis, R. W. B. (1950). *Brit. med. J.*, **1**, 85.
Foll, C. V. (1958). In press. *J. Trop. Pediat.*
Provis, H. S. and Ellis, R. W. B. (1955). *Arch. Dis. Childh.*, **30**, 328.
Simmons, K. and Greulich, W. W. (1943). *J. Pediat.*, **22**, 518.
Wilson, D. C. and Sutherland, I. (1949). *Brit. med. J.*, **2**, 130.
——, —— (1950). *Ibid.*, **2**, 862.

THE PREVALENCE OF DENTAL CARIES IN RELATION TO MATURITY

BY

J. N. MANSBRIDGE

From the Department of Public Health and Social Medicine, University of Edinburgh

(RECEIVED FOR PUBLICATION MARCH 27, 1958)

This study constitutes part of an investigation of the epidemiology of dental caries in 4,034 Edinburgh children in the age range 5-17 years. Of this total sample, 1,730 children were examined as part of a joint investigation with H. S. Provis and R. W. B. Ellis, who were making an anthropometric study of the children (Provis and Ellis, 1955). Therefore for this group of children data relating to certain anthropometric measurements were available in addition to the dental findings.

As socio-economic factors often influence growth, it was decided that a proportion of this sample of children should derive from private, fee-paying schools. Because of the influence of these factors on growth, it seemed not unreasonable to suppose that they could also influence dental health. When the dental state of children from fee-paying schools was compared with that of an otherwise comparable group of children from non-fee-paying schools differences in dental caries experience were found to exist. Thus, in the deciduous dentition, prevalence of dental caries was found to be lower among the fee-paying than amongst the non-fee-paying group, while in the permanent dentition the reverse was observed ; that is, dental caries was now found to be more prevalent among the fee-paying than among the non-fee-paying children. Furthermore, it was also found that the proportions of the various tooth surfaces attacked by caries differed between these two classes of children.

Analysis of the data suggested that independent aetiological factors operate in differing degree in the two contrasting social groups and these findings, supported by evidence from the literature, suggest the view that these effects reflect poorer structural quality of the teeth in the lower social class and a more caries-provoking diet of children from a higher social class environment.

Thus, by selection, the children compared were in the main divided into those belonging predominantly to Social Class I, while the remainder (the non-fee-paying children) represented Social Classes III, IV and V (Registrar General, 1931). This division of the sample distinguished unmistakably two distinct groups of differing social environments. The information available relating to the occupation of the child's father was in most instances insufficiently precise to discriminate between the various social levels of which the non-fee-paying children were comprised. For this reason these children constituted a socially heterogeneous group.

It is well recognized that differences in both stature and weight of children vary according to socio-economic level and, since such variation is probably related to standards of diet and nutrition, the possibility existed that physical differences within the non-fee-paying group of children might discriminate between the various social strata of which the group was composed, in terms of diet and nutrition.

Clements (1953) examined data relating to heights and weights of British children over the past 70 years. These data show clearly the differences that exist in height and weight between children drawn from upper, middle and lower income groups, and also indicate that children are growing more quickly now than they were some years ago. Furthermore, while these changes have taken place in all social groups, the greatest increases have occurred in the lower income groups, with the result that the disparity between children from upper and lower income groups has now been greatly reduced. Of considerable interest is the fact that during both world wars this upward trend was interrupted, to be continued again after World War I during the inter-war period. This effect of both world wars is interesting for Sognnaes (1948) showed that during both wars there was a considerable reduction in the prevalence of dental caries in those countries involved. This reduction in caries was considered to be related to dietary changes, particularly those in regard to sugar consumption. He also showed that at the end of the wars after a delay of some years the prevalence of dental caries began to increase and continued towards the pre-war level.

Since, for this sample of Edinburgh school children, there were available data relating to lying height, nude weight and a clinical assessment of sexual maturity, it was decided that a comparison of dental caries experience with certain physical measurements of non-fee-paying children should be undertaken in order to see whether the differences in dental caries found between fee-paying and non-fee-paying children would be repeated between children of differing physique.

The literature revealed only two investigations in which the relationship between physique and dental caries was studied. Cunningham (1934), in an investigation of the relation of dental caries to disease, menstrual experience and physical measurements in 11,117 young women aged 15 to 19 years, found some evidence that the tall women showed a higher prevalence of dental caries than those of medium or short stature. This difference was found to be statistically significant.

Discussing these findings, she expresses the view that many of the women of 15-18 years may not yet have attained full stature, and since dental caries increases with age, it was possible that the taller women were also among the oldest in the sample. It is unfortunate that no attempt was made to study the age distribution of these women.

Hurme (1936), in a study of 54 case histories of first-year students, in which prevalence of caries, height and health records were compared, found that when the number of D.M.F. teeth (decayed, missing and filled) was compared with height, the relationship, although not well marked, showed the number of D.M.F. teeth to be slightly less in the shorter half of the group. However, when the extremes of the distribution were compared, the short individuals had fewer D.M.F. teeth than the tall. Furthermore, since most of the tall individuals happened to belong to the youngest age group, the difference between the tall and the short was obviously not a function of chronological age in this instance.

The discrepancy between chronological and developmental age in individual children can be considerable and in consequence differences can exist between the number of teeth erupted at any given age. Therefore differences in total dental caries experience in children at the same age may be due in part to this. Also, even when all teeth have erupted, some individuals will have had their teeth exposed in the mouth to risk of attack for a longer period than others of the same chronological age.

Boas (1933) presented data to show that in a homogeneous social group, development of the dentition and general physical development as measured by height are associated. Talmers (1952) also observed that children of both sexes who had erupted their second molars early, were usually advanced in both height and weight for their age. Conversely, those children who were late in eruption of the second molars were below average in height and weight. It was also noticed that the relationship between body size and eruption was more marked among the boys than among the girls.

Clearly, then, any association found between prevalence of dental caries and physique might also be explained by differences in the rate of development, rather than by absolute differences in physique.

Methods

The Sample. This has been described previously (Provis and Ellis, 1955).

Measurement of Dental Caries. The children were examined in the schools during school hours. The dental examinations were conducted using plane mouth mirrors and Ash No. 54 probes, and illumination was obtained by the use throughout of a portable lamp, using a 60-watt bulb. The dental findings were dictated to an assistant who recorded them on a standard dental chart.

The D.M.F. index (Klein, Palmer and Knutson, 1938) has been used to measure the prevalence of dental caries of the permanent teeth in these children. Using this index, the dental caries experience of an individual is expressed in the sum of all decayed, missing and filled permanent teeth, thus past experience of the disease in terms of treatment, i.e. extractions and fillings, is included with present untreated carious teeth to give the total caries experience of the individual at the time of examination.

Analysis. As a preliminary step in order to see whether or not any relationship existed between the incidence of dental caries and height and weight, the children were ranked in order of the greatest to least height and similarly for weight, for each age and for both sexes separately. Each yearly age group was then divided into thirds and comparison of dental caries experience was made between the greatest third and the least third for height and weight separately.

Results. It was found that up to and including the age of 11 years in both sexes the differences in dental caries experience between the tallest and shortest and between the heaviest and the lightest were quite insignificant and inconsistent. However, from 12 to 17 years of age for both sexes the taller children showed a consistently greater number of D.M.F. teeth per child than those who were shorter at the same age, with one exception only; that was

in girls aged 17 years, where the shortest girls showed an appreciably greater average number of D.M.F. teeth per girl than the tallest.

When weight and dental caries experience were compared, the heaviest girls showed a consistently higher average number of D.M.F. teeth from 12 to 17 years than the lightest girls, but in boys the data showed less consistency and at 12, 13 and 17 years the lightest boys showed a higher average dental caries experience, but at 14, 15 and 16 showed the same trend as the girls, that is, the heaviest had the greatest D.M.F.

Figures 1 and 2 illustrate the differences in D.M.F. between these two groups and the numerical data are presented in Appendix Tables 1 and 2.

It was found that these differences could not be explained entirely on the basis of the numbers of teeth erupted, for the average number of D.M.F. teeth per 100 teeth erupted clearly indicated a higher incidence of caries in the taller and heavier children relative to the number of teeth erupted, compared with the shorter and lighter. Also, the differences in mean age of the children seemed inadequate to explain the differences shown in dental caries experience. As mentioned earlier, it was observed that under 12 years of age the differences in dental caries between the tallest and shortest and between the heaviest and lightest were both insignificant and inconsistent. This contrast and the age at which notable differences began to appear suggested the possibility that sexual maturation may exert some influence in the incidence of dental caries and be responsible for the differences in caries between groups of contrasting physiques.

The data relating to dental caries prevalence in the total sample of Edinburgh children indicated that the greatest increase in the annual increment of caries was found to occur in girls between the ages of 13 and 14 years and in boys between 15 and 16 years of age, a difference of two years (Appendix Table 3).

Provis and Ellis (1955), in a study of the same Edinburgh children, found that boys began to show evidence of sexual maturation on the average two years later than girls. The median age of pubescence in boys was 13·45 years and in girls 11·30 years, while the median age of adolescence was for boys 15·35 years and for girls 13·35 years.

It is apparent that the peak increase in dental caries and the onset of adolescence correspond in time for both sexes. The suggestion is strong, therefore, that these two events may be related in some way.

For these children a clinical assessment of sexual maturity, made by H. S. Provis, was available. Three grades of maturity were recognized, 'non-

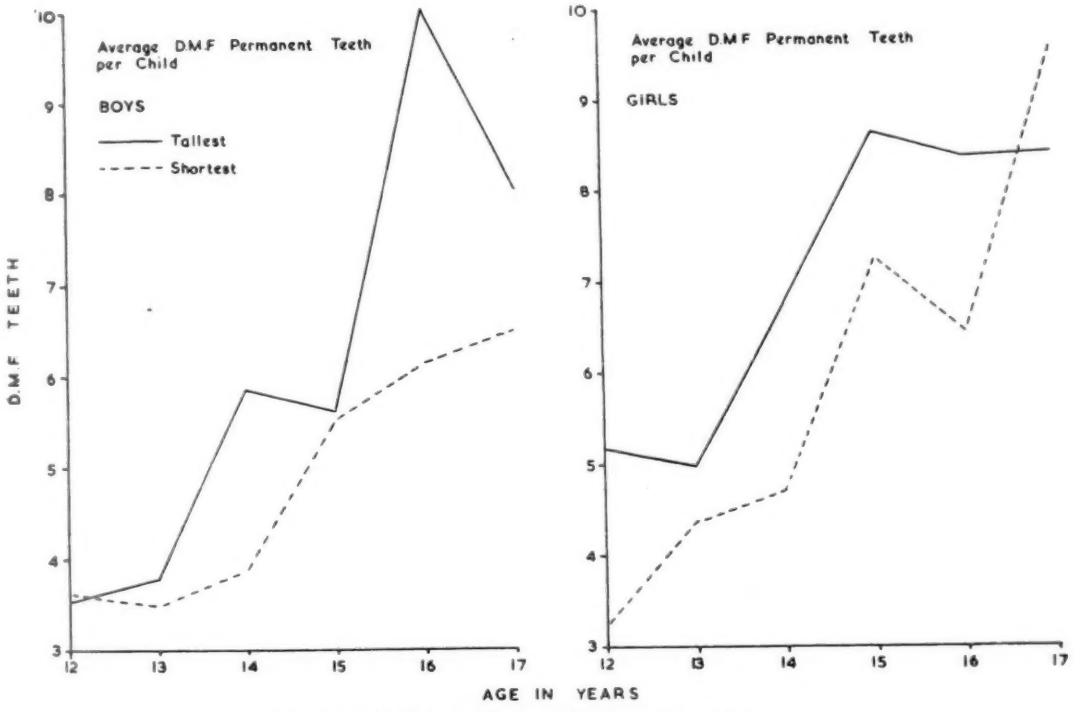


FIG. 1.—D.M.F. for tallest and shortest third of age group.

pubescent', with no evidence of sexual development, 'adolescent' as an advanced stage of maturity, while the 'pubescent' grade was intermediate. The assessment of maturity in boys was determined by the distribution of pubic and axillary hair, together with degree of development of the genitalia, according to the criteria of Ellis (1946). In girls, the beginning of pubescence was defined by breast enlargement, while the onset of menstruation was taken as the commencement of adolescence.

Therefore for each yearly group in the upper and lower thirds for height and weight, the data relating to degree of maturation were examined. These data are presented in Table 1 as combined totals for all age groups and are also given in greater detail in Appendix Tables 4 and 5.

It can be seen from these data that a very much larger proportion of the children in the upper thirds for both height and weight are in a more advanced stage of sexual maturation than those children who happen to be in the lower thirds.

To determine whether an association existed between sexual maturation and the incidence of dental caries, a comparison of dental caries experience was made between children of the same age but at different levels of maturation. For this purpose all the children for whom maturation data were available were taken as the sample.

TABLE 1
NUMBER OF CHILDREN IN THE DIFFERENT STAGES OF SEXUAL MATURATION

	Boys			Girls		
	NP	PB	AD	NP	PB	AD
Tallest ..	15	51	49	—	34	77
Shortest ..	58	39	18	13	38	40
Heaviest ..	14	53	48	—	29	82
Lightest ..	72	32	11	17	40	64

NP = Non-pubescent. PB = Pubescent. AD = Adolescent.

A preliminary examination of the data had revealed differences in dental caries between pubescent and adolescent children at the same age. However, differences were also observed in the number of teeth erupted in the different maturity groups even at the same age (Appendix Table 6). These differences were not large and it was clear that they contributed in part only to the differences in dental caries. For this reason it was decided that comparison between the different maturity grades would be confined to those children who had erupted all permanent second molars. In this way comparison would be made between children of the same age and sex and in approximately an equal stage of dental development to examine the relationship, if any, between sexual maturation and the incidence of dental caries.

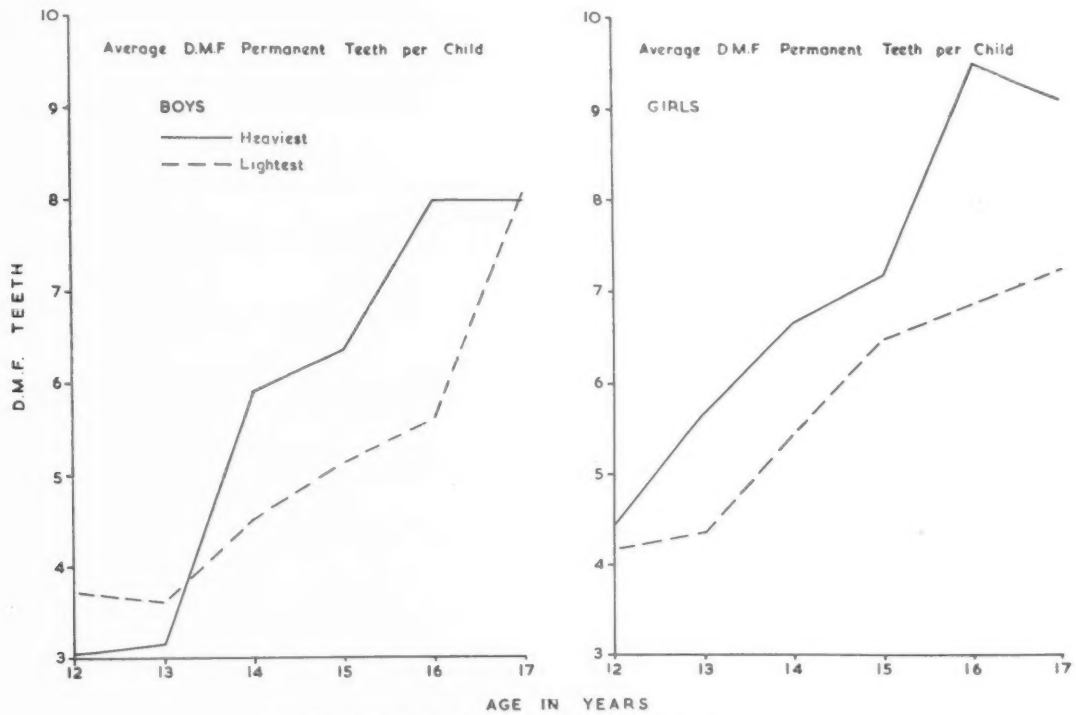


FIG. 2.—D.M.F. for heaviest and lightest third of age group.

When these requirements had been met, the distribution of children by age in each of the three maturity gradings was such that only two comparisons could usefully be made:

(1) Between 31 pubescent and 35 adolescent girls, aged 13 years, and
(2) Between 28 pubescent and 28 adolescent boys, aged 15 years.

The number of children in the non-pubescent group who had erupted all four second molars was, at any age, too small to justify comparison with a pubescent group of equivalent age.

It is generally recognized that attack of the teeth by dental caries is in part a function of the length of time that they are exposed in the mouth after eruption (Palmer, Klein and Kramer, 1938). Clements, Davies-Thomas and Pickett (1953) suggest that eruption of the second permanent molar and puberty are approximately coincident. It was considered possible, therefore, that differences in dental caries between children of the same age, who differed only in degree of maturation, might prove to be merely a reflection of the differences in time of eruption of the second molar. For example, it can be expected that the second molars of those children who are adolescent have been erupted in the mouth for a longer period than is the case of those children who are only pubescent at the same age. A second comparison was therefore made between the adolescent and pubescent children of both sexes in which the second molars were excluded from consideration. The results of these comparisons are presented in Tables 2, 3, 4 and 5.

It can be seen that those children who are less advanced in maturity have a smaller number of decayed, missing and filled teeth than those who are more mature at the same age. Furthermore, the adolescent children have an average number of D.M.F. teeth which more closely approximate that for the total Edinburgh sample at their age, while the pubescent children have an average more appropriate to a younger age.

The influence of the second molar upon the average number of D.M.F. teeth is considerable, but even when these teeth are excluded, a difference between the two maturity groups remains, which is in the same direction as before.

An examination of the distribution of dental caries of the individual teeth revealed no significant differences in distribution, that is, the pattern of attack in the two groups was substantially the same. The only difference observed was in amount of caries as indicated by the D.M.F. values in Tables 2 and 3. To test the possibility that differences in degree of dental caries might exist between the two maturity groups, the data were arranged to present dental caries measured in terms of affected tooth surfaces. The results indicated, however, that dental caries measured in this way shows differences between the groups equivalent to those observed when using the D.M.F. index. For these data then, the D.M.F. index provides a good measure of dental caries experience.

Thus far the evidence clearly suggests that degree of sexual maturation is associated in some way with the dental caries experience of the child. It was appreciated, however, that the number of children between whom comparison was made was of necessity small and, taking into account the high variability of dental caries in individuals, it was manifestly desirable that some measure of this possible association be obtained and tested. The comparison of dental caries experience between children in the greatest and least thirds of height and weight had shown that the difference in dental caries

TABLE 2
MEAN NUMBER OF DECAYED, MISSING AND FILLED TEETH IN 13-YEAR-OLD GIRLS

Maturity Grading	No.	Mean No. Teeth Erupted	Mean D.M.F. Teeth
Pubescent	31	27·42	4·81
Adolescent	35	27·28	5·40
Ungraded Total Edinburgh Sample	151	26·92	5·58

TABLE 3
MEAN NUMBER OF DECAYED, MISSING AND FILLED TEETH IN 15-YEAR-OLD BOYS

Maturity Grading	No.	Mean No. Teeth Erupted	Mean D.M.F. Teeth
Pubescent	28	27·68	5·68
Adolescent	28	27·53	6·54
Ungraded Total Edinburgh Sample	111	27·55	6·25

TABLE 4
MEAN NUMBER OF DECAYED, MISSING AND FILLED TEETH, SECOND MOLARS EXCLUDED, 13-YEAR-OLD GIRLS

Maturity Grading	No.	Mean D.M.F. Teeth
Pubescent	31	3·42
Adolescent	35	4·17

TABLE 5
MEAN NUMBER OF DECAYED, MISSING AND FILLED TEETH, SECOND MOLARS EXCLUDED, 15-YEAR-OLD BOYS

Maturity Grading	No.	Mean D.M.F. Teeth
Pubescent	28	4·36
Adolescent	28	4·79

in these children might also have been influenced to some extent by differences in both the number of teeth erupted and chronological age. The interrelationship of these possible factors presented a complicated situation and therefore, in an attempt to disentangle the effects of these various factors, multiple regression equations were calculated separately for boys and girls, in which the number of D.M.F. teeth was used as the dependent variate and some or all of the following in differing combinations were taken as independent variates:

Height	Maturity	
Weight	with stages:	Non-pubescent
Age		Pubescent
Number of teeth erupted		Adolescent

For this purpose, within the age range 11-17 years the entire sample for which these data were available was used and consisted of 629 boys and 581 girls. As might be expected, the number of D.M.F. teeth increased with age and with the total teeth erupted, these two indices being, of course, themselves highly correlated. When the effect of these was discounted, a marked difference appeared between the sexes. Among boys there was a highly significant increase of D.M.F. teeth with maturity, but there was no such effect with girls.

To investigate this further, the regressions were done in another way. In each year of age D.M.F. teeth were used as a dependent variate and the first and second stages of maturation (pubescent and adolescent) as independent variates. From the sums of squares and cross-products of these a pooled regression was done for boys and another for girls. The effect of this is to give a measure of the difference, over the range of ages studied, in number of D.M.F. teeth between children of like age according to which stage of maturation they had reached.

These regressions for both sexes showed that the number of teeth erupted was significantly associated with the stage of pubescence, but not with adolescence.

Discussion

It has been shown that differences in dental caries exist between those children who are tallest and heaviest and those who are shortest and lightest in the same yearly age group. However, these differences in physique could not be ascribed only to differences in standards of nutrition, if at all, and in consequence the original objective of this comparison, which was to discover whether differences in physique might discriminate between differing social levels, has not been achieved. It can be seen from the data presented in Appendix Tables 1 and 2 that the tallest and heaviest children were on average fractionally older and had a greater number of teeth erupted. In addition, it was found that the great majority of the tallest and heaviest children had reached a more advanced stage of maturity than those who were shortest and lightest.

With regard to the differences in dental caries between these children, it was appreciated that these differences could be due either to the greater number of teeth erupted, or to the slightly greater age of the tallest and heaviest children, or to both of these factors. However, neither of these seemed adequate to explain fully the observed differences in dental caries, although it was recognized that they could contribute in part. There remained, therefore, the generally more advanced maturity of the taller and heavier children as a possible factor in their greater prevalence of dental caries. It had also been observed that no consistent differences in caries experience existed between these two groups of children of contrasting physique up to 11 years of age, but that major differences were only found in the age group 12-17 years, during the period from puberty to adolescence. Furthermore, the data relating to the incidence of dental caries in the larger total sample of Edinburgh children indicated that the greatest annual increment of caries corresponded in time with the onset of adolescence in both sexes.

These facts therefore suggested that sexual maturation and susceptibility to caries may be associated in some way. A comparison between adolescent and pubescent children of the same chronological age, who had erupted all their second molars, revealed differences in dental caries for both sexes that seemed only attributable to differences in degree of sexual maturation, and further indicated that these differences involved the whole dentition, not only the more recently erupted second molars.

However, Parfitt and Parfitt (1954), in a study of the caries experience of a number of individuals from childhood to middle age, as derived from the records of private practice, presented data which showed no change in the caries incidence rate between the ages of 6-21 years, and commented that, while it has been suggested that puberty may have some influence on caries incidence rate, the data examined by them in their study did not show any such change. Of the 60 cases studied in this age range, 20 showed no change in caries incidence rate, but the remaining 40 individuals showed variations in the caries rate during this period, as many showing a decrease as an increase. They concluded, therefore, that puberty did not affect the caries incidence rate measurably.

The data provided by this study of Edinburgh children are insufficient to show what the mechanism involved in this phenomenon may be, but the find-

ings, together with evidence from other studies, suggest a possible explanation.

Boas (1933) presented data showing that in a homogeneous social group, development of the dentition and general physical development as measured by height are associated. He demonstrated that early dentition was related to early increase in stature.

Talmers (1952) also observed that children of both sexes who had erupted their second molars early were usually advanced in both height and weight for their age. Conversely, she found that those children who were late in eruption of the second molars were below average in height and weight.

Clements *et al.* (1953) found that there was a trend towards the earlier eruption of the lower C, PM_1 and M_2 teeth in those children who showed physical signs of puberty compared with those who showed no signs of puberty.

The data for Edinburgh children indicated that the tallest (and heaviest) children had a consistently greater number of teeth erupted than the smallest (and lightest) at approximately the same age, and are therefore in agreement with these other three studies. Also, the data given in Appendix Table 6, showing the average number of teeth found at various stages of physical maturation in both boys and girls, appear to confirm the view that tooth eruption and general physical development are closely related.

Of particular interest are the findings of Ellis (1946) in a study of height and weight in relation to onset of puberty in boys aged 11-16 years. He found that not only were boys of a higher maturity group heavier and taller than boys of the same age in a lower maturity group, but that difference between the growth curves could be demonstrated as far back as the sixth year. There is thus good evidence that general physical development and eruption of teeth are associated, and further, that those children who mature early have been early in general physical development from a much earlier age, while those in whom the onset of puberty is late, have been late in general physical development throughout their early years.

It seems possible to suggest, therefore, that in terms of dental development, those who mature late (e.g. in this study, boys who at 15 are classed as pubescent) may have been late in eruption of their teeth throughout their whole period of dental development. In consequence their teeth would have been exposed to risk of attack by dental caries for a shorter period than in the case of those children who have erupted their teeth at the usual times or earlier.

While the differences in decayed, missing and filled teeth between pubescent and adolescent children of the same age could be explained in terms of differences in times of dental development, the possibility exists that these differences in caries experience may be dietary in origin. The period of sexual maturity is accompanied by a rapid acceleration in growth and in consequence nutritional needs are increased, together with corresponding increase in appetite. Widdowson (1947) presents data from which it is apparent that caloric intake reaches a peak for boys at 15 years of age and for girls at 14 years.

Her data relating to total sugar consumption of children are also of some interest, showing that in boys, the highest average intake was 37·7 oz. per week at 15 years of age, and in girls 26·0 oz. per week at the age of 14 years. Total sugar consumption included sugar taken as such, sweets including chocolate, jams, cakes, biscuits, sugar in puddings and in cooked fruit. It was also found that up to the age of 8, differences in sugar consumption between the sexes were negligible, but from 9 years upwards boys consumed more than girls and at 15 they were eating nearly twice as much. Between 15 and 18 years boys ate more than twice as much as girls of similar age.

A finding of considerable importance was the very great variation in food consumption of children at the same age and the fact that these extreme variations were compatible with normal physical development. Ellis (1951), commenting upon this observation regarding variations in food consumption in individual children of the same age, poses the question as to whether maturity grading of children in such a study might not reveal less variation in caloric intake in relation to stage of maturity reached than was observed when the children were grouped by chronological age.

Since an increased intake of refined carbohydrate, especially sugar in sticky form between meals, has been shown to be associated with an increase in susceptibility to dental caries (Gustafsson, Quensel, Lanke, Lundqvist, Grahnén, Bonow and Krasse, 1954), the high consumption of these items of diet by children in the 13-15 years old age group suggests another possible explanation of the differences in dental caries found between pubescent and adolescent children of the same age. That is, those who mature physically early may then have subsisted for a longer period upon a diet containing a high level of refined carbohydrates than those of the same age who matured later. Gustafsson *et al.* (1954) clearly demonstrated the rapidity with which susceptibility to dental caries could be altered by increasing or decreasing the intake of sugars in certain forms, even in adults. These writers also pointed out that similar dietary changes in children might be expected to pro-

duce even more marked differences in susceptibility.

Although two quite different possible explanations may be offered to account for the differences in dental caries experience found in this study between pubescent and adolescent children, these explanations are not mutually exclusive. It is therefore possible that both differences in time of development of the dentition and differences in susceptibility due to dietary changes may both play their part in producing the results described in this study.

From the multiple regression analysis confirmation of previous findings in this study was obtained that, for boys, sexual maturity and dental caries incidence are associated and, more precisely, that this association is related to adolescence but not to pubescence. Furthermore, the differences in D.M.F. teeth between adolescent and pubescent boys of the same chronological age attributable to maturity alone was 1·8 teeth. For girls, however, the differences in dental caries experience between those who are adolescent and those who are pubescent at the same age were not found to be significantly associated with stage of maturity. It is of some interest that Talmers (1952) noted that the relationship between body size and eruption of second molars was less marked in girls than in boys.

This difference between the sexes was not expected since the previous evidence suggested that, if in fact sexual maturity and dental caries incidence were associated, it would have been so for both sexes inasmuch as:

(1) For the total Edinburgh sample the greatest increment of dental caries was found to correspond in time with the onset of adolescence in both sexes, i.e., between 13 and 14 years in girls and 15 and 16 in boys. It was seen, however, that the increase in D.M.F. teeth in boys between 15 and 16 was greater than the increase in girls between 13 and 14 years.

(2) The tallest and heaviest thirds of each yearly age group showed a significantly greater proportion of children in more advanced stages of maturity than those in the least thirds. This was true for both sexes.

(3) The comparison between pubescent and adolescent children of the same chronological age, who had also erupted all their second permanent molars indicated that there was a higher incidence of caries in the adolescent children of both sexes and that this difference in caries affected the dentition as a whole, not *only* the second molars.

It is recognized that individual variations in dental caries incidence are considerable and result in large standard deviations. Consequently because of this variability any difference in D.M.F. rates between groups of individuals must be large to be statistically significant. Taking all the evidence into account, the possibility exists that the difference in dental caries experience observed between girls at different stages of maturation may, in fact, be associated with maturity in much the same way as boys, even if not of such magnitude as to show a statistically significant relationship.

It is concluded, therefore, from the evidence obtained that adolescence in boys is associated with a higher dental caries incidence than is found in pubescent boys of the same age.

It is suggested that this may be due either to a longer total exposure of the teeth in the mouth or to dietary factors associated with adolescence, or to a combination of both factors together.

Finally, the regressions for both sexes provided statistical evidence that the number of teeth erupted was associated with pubescence. This confirms the observations made from the data presented in Appendix Table 6, and also those of Clements *et al.* (1953).

Summary and Conclusions

Data are presented which show a relationship between dental caries experience and stage of sexual maturation in children.

When children of the same chronological age and at an equal stage of dental development were compared, it was found that children further advanced in maturation showed a higher dental caries experience than those who were less advanced. Also this difference in dental caries appeared to influence the dentition as a whole.

Possible reasons for this are discussed.

From the evidence obtained in this investigation it is concluded that earlier sexual maturation is associated with an increased prevalence of dental caries in boys.

For girls no statistically significant evidence was obtained to indicate that a similar relationship exists, although other evidence suggests that this may be so.

Finally, it was also found that for both sexes those children who reach the stage of pubescence early have a greater number of permanent teeth erupted than non-pubescent children of the same chronological age.

I wish to thank Professor J. H. F. Brotherston and Professor R. W. B. Ellis for their most helpful advice and criticism. I am also indebted to Dr. H. S. Provis for his co-operation in this study, to Dr. W. N. Boog Watson, Chief School Medical Officer and Mr. G. Moody, Chief Dental Officer, of the City of Edinburgh, for their most helpful co-operation in the collection of the original data.

My sincere thanks are due to Dr. Barnet Woolf for his valuable statistical advice and to Miss M. Brown for her assistance in the computation of the raw data.

References

Boas, F (1933). *Hum. Biol.*, **5**, 429.
Clements, E. M. B. (1953). *Brit. med. J.*, **2**, 897.
-- —, Davies-Thomas, E. and Pickett, K. G. (1953). *Ibid.*, **1**, 1421.

Cunningham, R. L. (1934). *J. dent. Res.*, **14**, 439.
Ellis, R. W. B. (1946). *Arch. Dis. Childh.*, **21**, 181.
—— (1951). *Brit. J. Nutr.*, **5**, 151.
Gustafsson, B. E., Quensel, C. E., Lanke, L. S., Lundqvist, C., Grahnén, H., Bonow, B. E. and Krasse, B. (1954). *Acta odont. scand.*, **11**, 232.
Hurme, V. O. (1936). *J. dent. Res.*, **15**, 395.
Klein, H., Palmer, C. E. and Knutson, J. W. (1938). *Publ. Hlth. Rep. (Wash.)*, **53**, 751.
Palmer, C. E., Klein, H. and Kramer, M. (1938). *Growth*, **2**, 149.
Parfitt, G. J. and Parfitt, J. B. (1954). *Brit. dent. J.*, **96**, 183.
Provis, H. S. and Ellis, R. W. B. (1955). *Arch. Dis. Childh.*, **30**, 328.
Registrar General (1931). Classification of Occupations. H.M.S.O., London.
Sognnaes, R. F. (1948). *Amer. J. Dis. Child.*, **75**, 792.
Talmers, D. A. (1952). *N.Y. St. dent. J.*, **18**, 314.
Widdowson, E. M. (1947). *Spec. Rep. Ser. Med. Res. Coun. (Lond.)*, No. 257.

APPENDIX

TABLE 1
DENTAL CARIES IN RELATION TO HEIGHT

No.	Tallest Third				Shortest Third			
	Mean Age (yr.)	Mean No. Teeth Erupted	Mean No. D.M.F. Teeth per Child	D.M.F per 100 Teeth Erupted	Mean Age (yr.)	Mean No. Teeth Erupted	Mean No. D.M.F. Teeth per Child	D.M.F. per 100 Teeth Erupted
Boys								
23	12·6	25·7	3·5	13·7	12·5	23·8	3·4	14·2
24	13·5	26·5	3·8	14·3	13·2	25·2	3·5	13·9
24	14·5	27·6	5·9	21·3	14·5	26·4	3·9	14·7
21	15·4	27·8	5·6	20·2	15·2	27·2	5·4	19·7
13	16·6	28·5	10·1	35·3	16·4	27·7	6·1	22·2
10	17·5	28·6	8·1	28·3	17·4	28·7	6·5	22·6
Girls								
26	12·7	26·2	5·2	19·8	12·5	25·1	3·2	12·9
26	13·6	26·8	5·0	18·7	13·4	26·2	4·4	16·7
17	14·6	27·6	6·8	24·5	14·4	26·8	4·8	17·8
19	15·5	28·1	8·6	30·7	15·3	27·7	7·3	26·2
14	16·5	28·9	8·4	29·0	16·4	28·1	6·4	22·9
9	17·5	28·0	8·4	30·2	17·5	27·8	9·5	34·4

TABLE 2
DENTAL CARIES IN RELATION TO WEIGHT

No.	Heaviest Third				Lightest Third			
	Mean Age (yr.)	Mean No. Teeth Erupted	Mean No. D.M.F. Teeth per Child	D.M.F. per 100 Teeth Erupted	Mean Age (yr.)	Mean No. Teeth Erupted	Mean No. D.M.F. Teeth per Child	D.M.F. per 100 Teeth Erupted
Boys								
23	12·6	25·3	3·0	12·0	12·5	23·3	3·7	15·9
24	13·6	26·6	3·2	11·9	13·4	24·8	3·6	14·6
24	14·5	27·7	5·9	21·4	14·5	26·6	4·5	17·1
21	15·4	27·6	6·4	23·1	15·2	27·3	5·1	18·8
13	16·6	28·1	8·0	28·4	16·4	27·8	5·6	20·2
10	17·4	28·8	8·0	27·8	17·4	28·6	8·1	28·3
Girls								
26	12·6	26·2	4·4	16·9	12·5	25·2	4·2	16·8
26	13·6	27·1	5·6	20·8	13·3	26·1	4·3	16·6
17	14·5	27·3	6·6	24·3	14·4	26·8	5·5	20·6
19	15·5	28·1	7·2	25·5	15·3	27·6	6·5	23·7
14	16·6	28·6	9·5	33·2	16·4	28·2	6·9	24·3
9	17·6	28·3	9·1	32·2	17·4	27·8	7·2	26·0

TABLE 3
DENTAL CARIES PREVALENCE BY AGE AND SEX IN A SAMPLE OF 4,034 EDINBURGH CHILDREN

Age (yr.)	Boys			Girls		
	No.	Mean D.M.F. Teeth per Child	Annual Increment in Mean D.M.F. Teeth	No.	Mean D.M.F. Teeth per Child	Annual Increment in Mean D.M.F. Teeth
5	135	0·12	0·00	144	0·19	0·00
6	200	0·65	0·53	170	0·70	0·51
7	170	1·69	1·04	171	2·13	1·43
8	204	1·83	0·14	202	2·31	0·18
9	192	2·20	0·37	193	2·64	0·33
10	183	2·64	0·44	204	3·12	0·48
11	207	3·41	0·77	218	4·17	1·05
12	199	4·10	0·69	205	4·71	0·54
13	123	4·47	0·37	151	5·58	0·87
14	117	5·15	0·68	133	7·11	1·53
15	111	6·23	1·08	119	7·73	0·62
16	69	7·97	1·74	90	8·63	0·90
17	62	8·11	0·14	62	9·11	0·48

TABLE 4
THE NUMBER AND PERCENTAGE OF BOYS IN THE VARIOUS STAGES OF SEXUAL MATURATION

Age Group	Number						Percentage					
	NP	PB	AD	NP	PB	AD	NP	PB	AD	NP	PB	AD
	Tallest			Shortest			Tallest			Shortest		
12	11	12	—	22	1	—	48	52	—	96	4	—
13	4	19	1	21	3	—	17	79	4	87	13	—
14	—	18	6	13	10	1	—	75	25	54	42	4
15	—	2	19	2	16	3	—	9	91	9	77	14
16	—	—	13	—	8	5	—	—	100	—	62	38
17	—	—	10	—	1	9	—	—	100	—	10	90
Total	15	51	49	58	39	18	13	44	43	50	34	16
	Heaviest			Lightest			Heaviest			Lightest		
12	10	13	—	23	—	—	43	57	—	100	—	—
13	4	19	1	22	2	—	17	79	4	92	8	—
14	—	17	7	16	8	—	—	71	29	67	33	—
15	—	4	17	3	16	2	—	19	81	14	77	9
16	—	—	13	—	8	5	—	—	100	—	62	38
17	—	—	10	—	1	9	—	—	100	—	10	90
Total	14	53	48	64	35	16	12	46	42	56	30	14

NP = Non-pubescent. PB = Pubescent. AD = Adolescent.

TABLE 5
THE NUMBER AND PERCENTAGE OF GIRLS IN THE VARIOUS STAGES OF SEXUAL MATURATION

Age Group	Number						Percen age					
	NP	PB	AD	NP	PB	AD	NP	PB	AD	NP	PB	AD
	Tallest			Shortest			Tallest			Shortest		
12	—	21	5	9	17	—	—	81	19	35	65	—
13	—	9	17	3	16	7	—	35	65	12	61	27
14	—	3	14	1	4	12	—	18	82	6	24	70
15	—	1	18	—	1	18	—	5	95	—	5	95
16	—	—	14	—	—	14	—	—	100	—	—	100
17	—	—	9	—	—	9	—	—	100	—	—	100
Total	—	34	77	13	38	60	—	31	69	12	34	54
	Heaviest			Lightest			Heaviest			Lightest		
12	—	22	4	13	11	2	—	85	15	50	42	8
13	—	5	21	3	20	3	—	19	81	12	76	12
14	—	2	15	1	6	10	—	12	88	6	35	59
15	—	—	19	—	3	16	—	—	100	—	16	84
16	—	—	14	—	—	14	—	—	100	—	—	100
17	—	—	9	—	—	9	—	—	100	—	—	100
Total	—	29	82	17	40	54	—	26	74	15	36	49

NP = Non-pubescent. PB = Pubescent. AD = Adolescent.

TABLE 6
MEAN NUMBER OF TEETH ERUPTED PER CHILD AND ASSESSMENT OF SEXUAL MATURATION

Age (yr.)	Assessment of Sexual Maturity	Boys		Girls	
		No.	Mean No. of Teeth Erupted	No.	Mean No. of Teeth Erupted
11	Non-pubescent	—	—	29	21·69
	Pubescent	—	—	34	24·09
12	Non-pubescent	70	24·14	13	25·69
	Pubescent	21	25·90	67	25·60
	Adolescent	—	—	7	26·71
13	Non-pubescent	42	25·55	—	—
	Pubescent	43	25·98	39	26·79
	Adolescent	—	—	46	27·04
14	Non-pubescent	19	26·58	—	—
	Pubescent	53	27·28	13	26·54
	Adolescent	15	27·47	54	27·46
15	Pubescent	35	27·34	—	—
	Adolescent	52	27·69	—	—

FAMILIAL DYSAUTONOMIA

BY

T. McKENDRICK

From the Paediatric Unit, Hillingdon Hospital, Middlesex

(RECEIVED FOR PUBLICATION APRIL 11, 1958)

Familial dysautonomia is a rare syndrome of childhood affecting the nervous system. As the name suggests, dysfunction of the autonomic system is a prominent feature. It was first recognized as a separate entity by Riley, Day, Greeley and Langford (1949), the first large series being described by Riley (1952). So far, about 70 patients have been recorded. Though the fully developed syndrome is unmistakable, not all its features can be elicited in infancy and it is likely that some patients have died undiagnosed. Some of the constituent features may suggest other commoner diseases such as fibrocystic disease of the pancreas, cerebral palsy or childhood schizophrenia. There may therefore be further patients as yet unrecognized in long stay hospitals or mental deficiency institutions, or attending psychiatric clinics. These unfortunate children and their families can be helped (Riley, 1957) so that early recognition is important.

With the exception of one from Vienna (Tyndel, 1955), all the cases so far recorded have been from America or Canada (Forster and Tyndel, 1956). The following example is unusual in that the diagnosis was certain at the age of 8 months despite the absence of a family history of this condition.

Case Report

B.A. is the third child of Jewish parents. When she was born her father was aged 41 and her mother 39. Both had been healthy and there was no history of consanguinity. Their first child, a boy of 16, and their second, a girl of 10½, were healthy and had both been breast fed for about nine months. B.A. was born at term by uncomplicated breech delivery following moderately severe maternal pre-eclampsia in the last month of pregnancy. Her birth weight was 6 lb. 4½ oz. She showed mild asphyxia at birth, but the only other abnormality noted then was that the fourth toe of each foot tended to cross medially under the third. Breast feeding was not established as the baby never sucked properly.

Advice was sought when she was 8 months old because of the following symptoms:

(1) Coldness of the extremities since the first few days of life and always present irrespective of clothing, room temperature or weather. Her hands and feet were frequently blue with cold, and sometimes swollen.

(2) Profuse sweating from her head and body since coming home from the maternity hospital. She invariably needed a complete change of dress and bed clothes each morning.

(3) Feeding difficulty had been present since birth and appeared to be due to dysphagia. Since the age of 1 month she began to put her thumb into her mouth after each mouthful of feed, apparently to assist swallowing. As a result, each feed took an hour or more and many were never finished. She frequently spat out or refused feeds, and never seemed hungry. Solids were consistently refused.

(4) Breath-holding attacks. These began at the age of 5 months and had increased in frequency from one or two to three or four daily. Either without warning or whilst crying, she would hold her breath, become cyanotic and lose consciousness for a few seconds. No sequelae had been noted.

(5) Emotional instability. She was easily and unpredictably upset, and to a much more profound degree than were her siblings at the same age. Sometimes she could not be consoled.

In spite of her discomfort and frustration, however, she had never produced any tears. There had been no vomiting, no excessive dribbling and her bowel actions were normal. There was no history of intercurrent illness, and she had never apparently been febrile. Her weight gain, though slow, had been fairly constant. She did not smile until 4 months old. Shortly after this she began to try to hold her head up, but at 7 months she was not sitting and made little attempt to play with toys.

Examination. B.A. was miserable but lusty. In spite of loud cries of misery and fear, there were no tears, though her conjunctivae were moist. Her hands were constantly active, but the movements were those of a child of 4 or 5 months of age. Throughout the examination she frequently interrupted her wailing by pushing her left thumb in her mouth to suck it only a few times before resuming her cries. There was mild plagiocephaly and slight asymmetry of the ears. The pulse was regular at 164 per minute. The heart was clinically normal, a quiet, short, blowing, apical mid-systolic murmur being considered physiological. Blood pressure: (whilst awake, by flush method) systolic 120 mm. mercury in arm, 90 mm. in leg; (whilst asleep, by auscultation) 106/60 mm. in arm, 80/50 mm. in leg. Though the hands and feet were abnormally cold and blue, the radial and tibial pulses were easily palpable. The trunk and limbs showed

cutis marmorata but her scalp and neck were wet with perspiration. No abnormality was found in the chest, abdomen, genitalia, ears, or nose and no enlarged glands were felt. The limbs showed full ranges of movement.

An examination of the nervous system showed that the fundi and pupillary reactions were normal. There was absence of corneal reflexes, associated with hypo- or anaesthesia of the corneae; some sensation was present in the rest of the area supplied by the trigeminal nerve, but the child did not resent a swab soaked in ammonia being held under her nose, nor did this produce any tears. The movement of the eyes and face was normal. There was a brisk gag reflex. Abnormal swallowing mechanism was noticed: a bolus of food when placed on the back of the tongue would be swallowed with an effort in two to three seconds; elsewhere in the mouth it was rejected. The limb movements were immature and there were no tendon reflexes present in arms or legs.

Developmental Assessment. (Gesell.) Made at 35 weeks by Dr. E. P. G. Michell. "The developmental profile was uneven and showed retardation in all areas. Gross motor performance was particularly affected; fine motor adaptive, less so. Predominantly, test behaviour was at the 20-24 week level."

Investigations. There were no cells, casts, albumen or organisms in the urine. A pooled specimen over several days showed no abnormal amount of pressor amines. Haemoglobin was 80%; white cells, 18,700 per c.mm., polymorphs, 39%; lymphocytes, 56%; monocytes 4%; eosinophils, 1%. Blood urea, 29 mg. per 100 ml.; blood cholesterol 105 mg. per 100 ml.; serum calcium, 9·6 mg. per 100 ml.; serum alkaline phosphatase 24·8 K-A units per 100 ml.; serum sodium, potassium, chloride and bicarbonate levels normal; plasma electrophoretic pattern within normal limits. The Wassermann reaction was negative; a Mantoux test 1 in 1,000 was negative. Electrocardiogram rate 165 per minute; sinus rhythm; P.R. 0·11 second; Q.R.S. 0·04 second; electrical axis vertical; there was less evidence of right ventricular preponderance than is usual at this age; ST segments and T waves were within normal limits. Radiographs of the chest and abdomen were normal. Bone development was compatible with age. A barium swallow was normal. Cerebrospinal fluid was clear and colourless; sugar, chlorides and protein were all within normal limits; there was no excess of globulin. Lange showed no reaction. An electroencephalogram showed no evidence of any paroxysmal disturbance or unilateral cerebral lesion. Subcutaneous injection of 0·125 mg. neostigmine bromide produced a few tears (Kroop, 1956).

Progress. During her 10-day stay in the ward she was kept in a cubicle of average temperature 70° F. The extremities became pink and warm. The rectal temperature varied irregularly between 97·0 and 100·2°F. When she was asleep the pulse was usually 120 per minute but when she was awake it was contantly raised to 160 per minute. She had three short breath-holding attacks, all related to examination or handling by nursing staff. Feeds continued to take an hour or more and many were left unfinished. Her weight remained about 14¾ lb.

She was discharged receiving phenobarbitone gr. ¼ twice daily. Subsequently there were only about six breath-holding attacks during the following 10 weeks. The blood pressure has once been as high as 146/86 mm. of mercury. One attack of bronchitis lasting three weeks occurred at the age of 9 months. At the age of 1 year she was less miserable than before admission. Developmental assessment (Gesell) at 53 weeks by Dr. E. P. G. Michell showed a similar pattern to that at 35 weeks. Her performance was on the whole at the 28-32 week level, but one test was performed at the 40-week level. At this time she began to show indifference to painful stimuli.

Discussion

This child shows many of the features of the syndrome as described in the literature. Other common but not essential features are not present and some cannot be assessed. Table 1 summarizes these.

TABLE 1

Feature	Present	Not Present	Not Fully Assessed
Hereditary factors	Jewish parents	Occurrence in siblings Consanguinity of parents	
Autonomic dysfunction	Absence of tears Excessive sweating Paroxysmal hypertension Poor control of peripheral circulation Abnormal swallowing mechanism	Skin blotches Bowel upsets Excessive dribbling Attacks of high fever	Postural hypotension
Voluntary motor-disturbance	Poor co-ordination Absent tendon reflexes	Orthopaedic deformity	Dysarthria
Sensory disturbance	Corneal anaesthesia		Indifference to pain Dysaesthesia Proprioceptive disturbance
Psychological features	Breath-holding attacks Emotional lability Retarded development	Vomiting attacks	
Other features	Retarded growth	Frequent respiratory infections Corneal ulceration	Tendency to accidental injury

She also had the typical facial expression, difficult to describe adequately, but apparently compounded of suspicion, fear and misery.

Of this diverse collection of symptoms, some are present so frequently as to be considered essential to the diagnosis. These are: (1) Jewish ancestry. (2) Reduced tear secretion. (3) Excessive sweating. (4) Feeding difficulty. (5) Cold hands and feet. (6) Postural hypotension. (7) Poor motor co-ordination. (8) Corneal anaesthesia. (9) Relative indifference to pain, and (10) Emotional lability.

A variable number of the other features in the table may be present. Also occasionally reported have been persistent leucocytosis, neonatal flaccidity and persistent thumb sucking. The predominating features tend to vary with age. Thus feeding difficulty is commonly the earliest symptom; absence of tears is not noteworthy before 2 months of age; motor inco-ordination is seldom appreciated before 6 months. After the age of 6 months breath-holding attacks begin, and parents may focus attention on apparent mental retardation or on excessive dribbling. Vomiting attacks usually predominate in those aged 2 to 5 years. Sensory disturbance and postural hypotension can be evaluated only after infancy.

The diagnosis in extreme infancy is not easily made, and usually doubt remains throughout the first year of life. Riley (1957) suggests that in the neonatal period at least the following should be present: (1) Family history. (2) Pronounced feeding difficulty and (3) Lack of deep tendon reflexes.

Family history, however, can never be more than suggestive, and has been found in only about a third of all cases so far reported. Feeding difficulty is common in newborn infants but in this condition it is marked and frequently shows no sign of ameliorating for several months. Though swallowing is more commonly reported to be abnormal, difficulty in sucking has also been noted. Tendon reflexes are not always absent in older cases. In some they vary from time to time, and it may be that they disappear as the child grows.

Moloshok and Reuben (1954) were able to gather the neonatal histories of 14 of their patients. They found that apart from feeding difficulty there was a high incidence of apnoeic or cyanotic attacks simulating atelectasis, hypothermia, attacks of high fever, excessive oral secretion, vomiting and failure to thrive. The present case suggests that profuse sweating and poor circulatory control may also occur in the neonatal period.

Differential Diagnosis. Provided that it is considered, familial dysautonomia is unlikely to be confused with other conditions. There are, however, points of similarity with several commoner diseases in infancy. Thus the vasomotor instability, sweating, hyporeflexia and misery occur also in pink disease. This condition, however, rarely affects children under the age of 6 months, whereas dysautonomic children are abnormal from birth. Photophobia, severe skin irritation and increased urinary excretion of pressor amines (Farquhar, Crawford and Law, 1956) often found in pink disease, have not been described in dysautonomia. In the latter, feeding difficulty as opposed to anorexia is typical.

Because of frequent lower respiratory infections, poor nutritional state, sweating, hypotonia and febrile episodes, fibrocystic disease of the pancreas may be suspected. Suspicion may be heightened by radiographic demonstration of areas of consolidation, atelectasis or emphysema. These are usually attributed to aspiration of food or vomitus as a result of inco-ordinated swallowing. Moloshok and Moseley (1956) have suggested that increased bronchial secretion may be responsible, much as the changes in fibrocystic disease are related to the unduly viscid secretion throughout the respiratory tree. Though the duodenal juice may be viscid and scanty in dysautonomia, pancreatic function is normal (Shwachman, Leubner and Catzel, 1955).

Cerebral palsy may show similar motor defects but sensory and vascular disturbances are not marked. Rarely, absence of tears may be due to congenital absence of the lachrymal glands, sometimes associated with other congenital defects in the face, skull or cranial nerve nuclei (Sjögren and Eriksen, 1950).

Later in childhood several other conditions require differentiation. The attacks of fever, vomiting, abdominal pain, headache and sweating may simulate the periodic syndrome. In this condition and in migraine, however, there are usually no physical signs.

Less easy to disprove is the presence of a phaeochromocytoma. Smid and DuShane (1955) could find fewer than a dozen under the age of 10 recorded in the literature. Both a phaeochromocytoma and dysautonomia may produce paroxysms of headache, pallor, sweating, abdominal pain, peripheral vasoconstriction and hypertension. Phaeochromocytoma, however, is not accompanied by nervous abnormalities and the attacks respond well, if temporarily, to adrenolytic agents such as phentolamine or piperoxane; there is also a great increase in urinary excretion of pressor amines.

Many of the psychological features of dysautonomia may superficially resemble those of schizophrenia. Exaggerated response to emotional stress,

withdrawal from surroundings in vomiting attacks, often with repetitive or self-injurious behaviour and apparent inability to concentrate, may all be seen in both conditions. Schizophrenic children may also show poor vasomotor control, muscle inco-ordination, and apparently retarded development. Examination, however, shows that dysautonomic children are not psychotic, nor is there any history suggesting precocious development followed by regression.

Finally some children with congenital indifference to pain have been described with absent tendon reflexes and retarded development, but there the similarity to dysautonomia ends.

Prognosis. The outlook as regards survival is uncertain. About a fifth of all the recorded cases have died, some in the first year of life, others in childhood. Most of the deaths seem to have been due to respiratory infection, with or without hyperpyrexia. At least one has been attributed to renal damage, and one child died following a haematemesis.

Of the survivors, the pattern of early development is becoming fairly well defined. Affected children remain below average height and weight. Their lives are punctuated by frequent illness and injury. The latter may begin with teething: by a combination of habitual rubbing of the tongue or cheek on teeth and indifference to pain, severe ulceration may result. Besides respiratory infection, corneal ulceration due to defective lachrymation is common. Motor performance is severely handicapped by inco-ordination and development is therefore retarded. Adaptation to these disabilities is poor.

No less a handicap is the psychological abnormality. The cycle of personality traits and their reactions in the family are described by Freedman, Helme, Havel, Eustis, Riley and Langford (1957). In infancy the situation is relatively simple. The affected infant is likely to be miserable and to show exaggeration of infantile reaction to stress. The case described here suggests that this is not entirely resistant to sedative therapy, but little information on the subject is available.

Later in childhood a more complicated situation develops. These children, realizing that they have unique and incurable physical handicaps, make many demands on their parents and become tyrannical. Yet they lack initiative and remain over-dependent on others. They tend to become very attached to adults other than their parents, especially women, and are rarely friendly to other children. The parents, even when the diagnosis is known to them, tend to feel afraid of their child's symptoms and to resent them. Some parents even feel guilty. Most try to gratify the child's inordinate demands. Such appeasement, especially when variable, reduces the child's sense of security. To the difficulty of controlling the "milieu interieur" is added that of trying to compensate for a changing social environment, and the whole cycle is enhanced. Partial or complete rejection by one or both parents may result.

The long term outlook is not known. The oldest patient so far recorded was 23 years old in 1957 (Riley, 1957). She had not fully compensated for her disabilities. Other patients are thought to be developing renal damage due to hypertension. Adult cases have never been described. It is not inherently impossible that adaptation, both physical and psychological, can eventually take place.

Summary

The clinical findings in a Jewish girl, aged 8 months, with familial dysautonomia are reported. The diagnosis was suggested by absence of tears, excessive sweating, paroxysmal hypertension, poor peripheral circulatory control and dysphagia. Poor muscle co-ordination, absence of tendon reflexes and corneal anaesthesia indicated that there was also disturbance of motor and sensory systems. Breath-holding attacks, emotional lability, retardation of development and relative failure to thrive were also present. Diagnosis is on clinical grounds alone.

The differential diagnosis in infancy includes pink disease, fibrocystic disease of the pancreas, cerebral palsy and congenital absence of lachrymal glands and in older children the periodic syndrome, schizophrenia and phaeochromocytoma.

Dysautonomia is not necessarily fatal, but the physical difficulties and psychological disturbances in child and family make the rearing of the child difficult.

I am grateful to Dr. H. V. L. Finlay for his permission to publish this account and also for much helpful advice and criticism. My thanks are also due to Dr. E. P. G. Michell for the developmental assessment.

References

Farquhar, J. W., Crawford, T. B. B. and Law, W. (1956). *Brit. med. J.*, **2**, 276.
Forster, W. and Tyndel, M. (1956). *J. ment. Sci.*, **102**, 345.
Freedman, A. M., Helme, W., Havel, J., Eustis, M. J., Riley, C. M. and Langford, W. S. (1957). *Amer. J. Orthopsychiat.*, **27**, 96.
Kroop, I. G. (1956). *J. Pediat.*, **48**, 328.
Moloshok, R. E. and Moseley, J. E. (1956). *Pediatrics*, **17**, 327.
—— and Reuben, R. N. (1954). *J. Mt Sinai Hosp.*, **21**, 137.
Riley, C. M. (1952). *J. Amer. med. Ass.*, **149**, 1532.
—— (1957). *Advanc. Pediat.*, **9**, 157.
——, Day, R. L., Greeley, D. M. and Langford, W. S. (1949). *Pediatrics*, **3**, 468.
Shwachman, H., Leubner, H. and Catzel, P. (1955). *Advanc. Pediat.*, **7**, 257.
Sjögren, H. and Eriksen, A. (1950). *Brit. J. Ophthal.*, **34**, 691.
Smid, A. C. and DuShane, J. W. (1955). *Amer. J. Dis. Child.*, **90**, 81.
Tyndel, M. (1955). *Wien. med. Wschr.*, **105**, 189.

AUTOPSY FINDINGS IN A CASE OF PITUITARY DWARFISM

BY

A. T. SANDISON

From the Departments of Pathology, the University and Western Infirmary, Glasgow

(RECEIVED FOR PUBLICATION MARCH 20, 1958)

Although the condition of pituitary dwarfism has been recognized for some considerable time, there is still a relative lack of published autopsy findings and the following case is reported briefly for this reason.

Lack of hypophysial growth hormone (almost certainly elaborated in the alpha cells of the pars anterior) during infancy or childhood results in varying degrees of under-development which may range from obvious dwarfism to slight degrees of lack of normal stature. In some cases, so-called primordial dwarfs may be small at birth and grow at a much reduced rate, while in others the child may grow normally for a varying period of time.

The term *infantilism*, sometimes used synonymously with dwarfism, may more strictly be applied to individuals in whom there is impairment of growth, sexual development and intellect while *nanism* implies restriction of growth in stature only. Infantilism is often referred to as the Levi-Lorain syndrome, the condition having been described by Lorain (1871) and by Levi (1908). Post-mortem studies are infrequent since the uncomplicated condition is not incompatible with good health. In childhood the patient is perfectly formed but somatic growth is slow. Development of the primary and secondary sexual phenomena does not occur at puberty and the genitalia usually remain infantile. This is not invariable, however, and some limited degree of sexual development may occur. Epiphyseal closure may be delayed but the ultimate stature attained is considerably below normal due to lack of growth hormone. Purely intellectual development may be satisfactory but emotional and behaviour patterns may be immature. These patients are slender with graceful limbs, ankles and wrists, and they often have fine, smooth skin and soft silky hair (Price, 1946).

Hypophysial dwarfs are usually born of normal parents, and some cases are recorded of hypophysial dwarfs producing normal offspring. They show good body symmetry, the physique being that of early childhood in which the lower measurements are relatively short. Most are thin and obesity is rather uncommon. The genitalia are generally under-developed and the secondary sexual characteristics may be absent or retarded. There may be amenorrhoea in the female and azoospermia in the male. Nevertheless, as indicated above, hypophysial dwarfs may occasionally be fertile. The skeletal framework is smaller and more fragile than normal and epiphyseal closure tends to be delayed. The appetite may be small and the basal metabolic rate low. There is not the profound impairment of the central nervous system noted in cretins, nor does one see the myxoedematous infiltration of subcutaneous or submucous tissues present in juvenile myxoedema. The metabolic consequences of adrenal hypoplasia are much less conspicuous than in Addison's disease. Glucose tolerance is sometimes increased. Occasionally radiography may show a small sella turcica but this is not common; indeed the sella may be enlarged due to adenoma or craniopharyngioma. It has been suggested that the term *ateleiosis* might well be used for the generality of dwarfism until the true extent of hypopituitarism in the causation of these cases is established (Cecil and Loeb, 1955).

For full consideration of types of dwarfism reference may be made to Wilkins (1950). Many of the points made above are confirmed and some further suggestions are put forward. Wilkins points out that androgen deficiency may be shown by low levels of 17-ketosteroids and by the relative absence of body hair. Often the testes and ovaries are immature and there is a low level of follicle-stimulating hormone. The facies is childish and immature but with attainment of the fourth decade a peculiar 'oldish-young' look may appear due to atrophy and wrinkling of the skin.

The pathology of this condition was first discussed by Erdheim (1916, 1925) who introduced the term

'nanosomia pituitaria'. Reference may be made also to Kraus (1926). Brief discussions are given in the textbooks of Cappell (1951) and Anderson (1953). Among the commoner causes of pituitary nanosomia are intra- or extra-cellular craniopharyngioma which may show marked retrogression. Other conditions described are fibrosis of the pars anterior (possibly ischaemic in origin), colloid-cystic degeneration, congenital syphilis, chronic hydrocephalus and hypophysial malformation. Russfield and Reiner (1957) have described three cases of dwarfism without mechanical destruction of the pituitary and postulate possible failure of production of growth hormone by so-called 'amphophil' cells. The thyroid gland may be atrophic but the parathyroids, which are probably not under hypophysial control, are unaffected. The adrenals may be small and occasionally diabetes mellitus or even diabetes insipidus has been described. The latter condition would suggest possible hypothalamic damage; hypothalamic damage may undoubtedly be responsible for obesity when this is present. It seems probable that lack of alpha cells leads to growth impairment while beta cell insufficiency is responsible for genital dystrophy. Cappell has pointed out that in the Lawrence-Moon-Biedl syndrome there is evidence of a hereditary influence, the dwarfism here being associated with retinitis pigmentosa and polydactyly.

In the case now to be described a 15-year-old girl died from malignant astrocytoma. An associated dwarfism was the result of pituitary hypoplasia and of the presence of chromophobe adenoma and developmental cyst in the small pars anterior.

Case History

The patient, a 15-year-old girl, was admitted to the wards of Dr. J. A. W. McCluskie at the Western Infirmary, Glasgow. She was the fifth child of normal parents, the siblings being normal, alive and well. Parturition was two months premature and the patient then weighed 1·6 Kg. Mental and physical growth was from the first retarded and all the landmarks of development were delayed in appearance. At the age of 22 months she weighed only 6·0 Kg. instead of the expected 11·0 Kg. At this time she was seen by Professor Stanley Graham at the Royal Hospital for Sick Children, Glasgow, and was then noted to be mentally backward. Her height was 65 cm. (normal 80 cm.) and the circumference of the head was 39 cm. (normal 47 cm.). The cranial sutures were well united. At this time a course of antuitrin G was given without obvious effect.

By the age of 30 months she could walk without aid but intelligible and coherent sentences were not formulated until the age of 7 years. During the four years before admission there had been little or no somatic growth but the patient was able to undertake simple domestic tasks. At the age of 13 years, for a period of three months only she menstruated, apparently normally, but thereafter amenorrhoea was invariable. There was, however, some development of secondary sexual characteristics.

Some five weeks before admission the patient fell heavily and was dazed for a short time. Two weeks later her behaviour suggested gross visual defect and she became inactive. Aphasia and incontinence then developed although after a time some capacity for speech returned.

On examination, the patient proved to be imbecile and uncooperative. The hands and feet were small, the maximum circumference of the head was 44 cm. and the distance from the anterior superior iliac spine to the internal malleolus was 55 cm. There was bilateral webbing of the second and third toes. The teeth were of primary dentition and in poor condition. The palate was normal, as were the ear drums. The left pupil was larger than the right; neither reacted to light and both lenses were rather opaque. The tendon reflexes were difficult to elicit but the plantar responses were flexor.

The erythrocyte sedimentation rate was 6 mm. in the first hour. The Wassermann reaction was negative. The white blood count was 16 500/c.mm. with a polymorphonuclear leucocytosis. A radiograph of the chest was negative: the skull was small but showed no abnormality; the bones of the forearm were normally ossified. Lumbar puncture showed an opalescent fluid under pressure. Cells were 650 polymorphs per c.mm. Sugar was 68·0 mg. %; protein, 160 mg. %; chlorides, 708 mg. %. There was no growth on culture and tubercle bacilli were not demonstrated. Despite intrathecal penicillin and oral sulphadimidine the condition of the patient deteriorated and she died 10 days after admission.

Post-Mortem Examination (Dr. J. M. Johnstone). The body length was about 120 cm., the mean for a girl of this age being 161 cm. The head, hands and feet were small but well-formed and the limbs in proportion to the trunk. The fingers were of 'spindle' type. The facial appearance was older than the stated age suggested. The trunk was rather obese and the breasts were low hemispheres with poorly developed nipples and areolae. On dissection they proved to be largely fatty. The pubic hair was normal but axillary hair was scanty.

The heart (110 g.) showed no congenital defects and the lungs (left, 120 g.; right, 95 g.) were normal. The alimentary tract, liver (440 g.), spleen (40 g.) and kidneys (each 30 g.) showed no evidence of acquired disease. The uterus was infantile and the ovaries small without obvious follicle or corpus luteum formation. The adrenals and thyroid were small. No parathyroid adenoma was discovered.

The brain was congested and the convolutions were flattened. There was bulging of the left frontal lobe; this proved to be due to a haemorrhagic, necrotic tumour with central cystic degeneration which occupied the whole frontal lobe, extended back to the left caudate nucleus and crossed into the right frontal lobe for a little way

FIG. 1.—Section of breast to show simple duct system without evidence of lobule formation. Haemalum and eosin. × 75.

via the anterior commissure. The optic nerves and chiasma appeared normal. The pituitary was small.

Histological Examination (A. T. Sandison). The heart, lungs, liver, spleen and kidneys showed no significant change. The pancreatic islets appeared normal. The thyroid acini contained abundant well-stained colloid and were lined by cuboidal epithelium. Parathyroid and adrenals showed no structural abnormality. The breasts were largely fatty but in the fibrous strands there were ducts of simple immature type without evidence of lobule formation (Fig. 1). The ovarian cortical stroma was only moderately cellular; a few small ripening follicles of immature appearance were seen. The cervix uteri was normal and the endometrium appeared inactive with some dilatation of the glands.

The cerebral neoplasm was a highly cellular, vascular and necrotic astrocytoma producing little or no glia. The cells varied from spheroidal to spindle-cell type but mitotic activity was not great.

PITUITARY. This was hypoplastic, the mid-level horizontal cross-sectional area being about two-thirds of that of some glands from females of similar age. The pars anterior was greatly congested with prominent vascular spaces. One lateral lobe was occupied by a rather haemorrhagic, trabeculated, small-cell chromophobe adenoma with protein-containing fluid between the trabeculae (Fig. 2). The chromophobe cells present

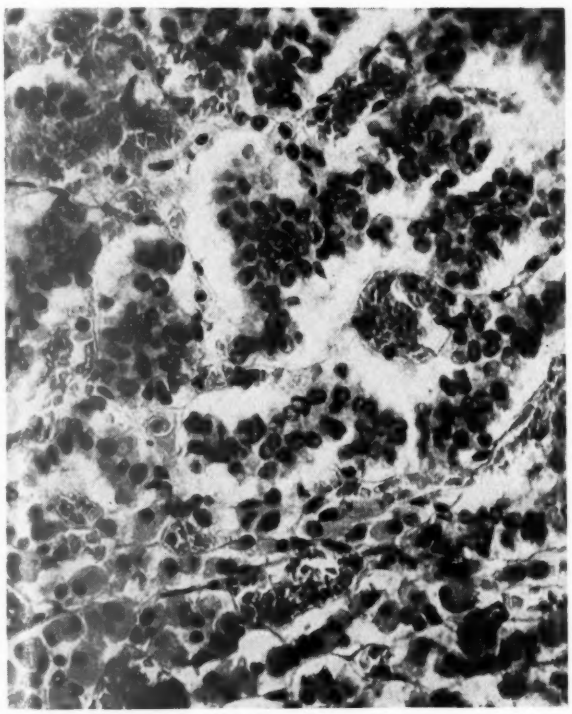


FIG. 2.—Chromophobe adenoma of pituitary with normal chromophil cells of pars anterior at the bottom. Picromallory stain. × 420.

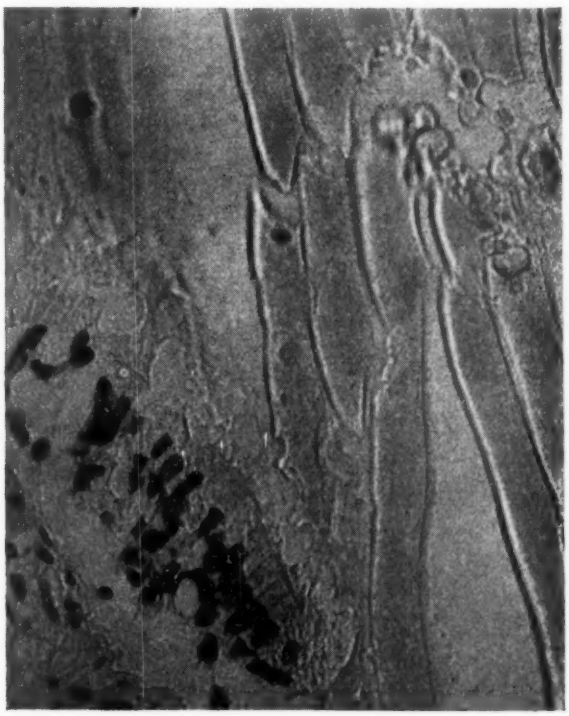


FIG. 3.—Developmental cyst of pars anterior containing colloid-like substance and lined by ciliated epithelium. Heidenhain's iron haematoxylin. × 420.

contained no granules stainable by the periodic-acid Schiff method. The opposite lateral area was largely occupied by a colloid-containing cyst which was lined partly by cubical and partly by tall columnar ciliated epithelium (Fig. 3). The remaining parenchyma contained well-granulated alpha and beta cells which were arranged rather haphazardly. The nature of these cells was confirmed by staining with the Mallory, phosphotungstic-acid haematoxylin, eosin-methylene blue and McLetchie and Pearse methods.

Discussion

The cause of death in this child was a malignant astrocytoma of the left frontal region which had produced obvious clinical effects for a period of six to seven weeks only. The patient, however, had been small at birth and had failed to grow normally; no increase in stature had been noticed in the four years before death. Mental development had also been retarded considerably although she could carry out simple domestic tasks. It is interesting to recall that the patient had menstruated three times at the age of 13 years but that this had not again occurred. Pubic hair developed despite the infantile genitalia but the breasts, although at first sight normal, were largely fatty. The normal developing breast at this age is a fibrous cone enveloped at the periphery by fat. Furthermore, the breast parenchyma was immature on histological examination.

The dwarfism here was of proportionate type and associated with mental retardation and poor development of sexual characteristics. This picture is not inconsistent with pituitary insufficiency and this was substantiated by histological examination. The pituitary in this instance was hypoplastic. Furthermore, a considerable bulk of the gland was occupied by a simple chromophobe adenoma and by a cyst of developmental Rathke type as shown by the ciliated lining. These abnormalities must have further reduced the volume of functional pars anterior. Undoubted alpha and beta cells were demonstrated in rather haphazard arrangement but these must have been inadequate for the production of sufficient growth hormone and gonadotrophins.

Summary

A 15-year-old girl who died of malignant astrocytoma was a dwarf of proportionate type from birth. There was also retarded mental development and poor sexual development. This dwarfism was the result of hypoplasia of the pituitary gland, the pars anterior of which was largely occupied by a simple chromophobe adenoma and a developmental cyst.

My thanks are due to Dr. J. A. W. McCluskie for permission to publish this case and to Dr. J. M. Johnstone for allowing me to quote from his autopsy records. I am also grateful to Mr. N. L. Russell for technical assistance and to Mr. W. Mason for the photographs.

References

Anderson, W. A. D. (1953). *Pathology*, 2nd ed. London.
Cappell, D. F. (1951). Muir's *Textbook of Pathology*, 6th ed. London.
Cecil, R. L. and Loeb, R. F. (1955). *Textbook of Medicine*, 9th ed. Philadelphia and London.
Erdheim, J. (1916). *Beitr. path. Anat.*, **62**, 302.
—— (1925). *Ergebn. allg. Path. path. Anat.*, **21**, 482.
Kraus, E. J. (1926). In Henke and Lubarsch *Handbuch der Spezielle Pathologischen Anatomie und Histologie*, **8**, 899.
Levi, E. (1908). *Nouv. Inconogr. Salpêt.*, **21**, 297, 421.
Lorain (1871). Lettre préfacée à la thèse de Faneau de la Cour. *Du féminisme et de l'infantilisme chez les tuberculeux*. Paris.
Price, F. W. (1946). *A Textbook of the Practice of Medicine*, 7th ed. London.
Russfield, A. B. and Reiner, L. (1957). *Lab. Invest.*, **6**, 334.
Wilkins, L. (1950). *The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence*. Springfield, Illinois.

INSUFFICIENT GLUCURONIDE FORMATION IN THE NEWBORN AND ITS RELATIONSHIP TO THE PATHOGENESIS OF ICTERUS NEONATORUM

BY

M. VEST

From the Children's Hospital, University of Basel, Switzerland

(RECEIVED FOR PUBLICATION FEBRUARY 24, 1958)

In the last few years the pathogenesis of icterus neonatorum and kernikterus has aroused renewed interest (Napp and Plotz, 1949; Obrinsky, Allen and Anderson, 1954; Billing, Cole and Lathe, 1954; Meyer, 1956). The discovery by Schmid (1956) and Billing, Cole and Lathe (1957) that bilirubin is excreted in the bile as a glucuronide now makes it possible to reinvestigate this problem more specifically. The accumulation of bilirubin in the blood after birth suggests that the excretory capacity of the liver is inadequate. Such an inadequacy has been demonstrated only indirectly, either by the diminished ability of newborn and premature infants to excrete bromsulphalein dye (Mollison and Cutbush, 1949; Yudkin and Gellis, 1949; Obrinsky, Denley and Brauer, 1952; Perl, 1957) or by the fact that an inverse relationship exists between the amount of bile pigment in the meconium and the subsequent rise of the bilirubin in the serum (Ross, Waugh and Malloy, 1937; Fashena, 1948; Napp and Plotz, 1949; Vest, 1958).

It therefore seemed promising to investigate the glucuronic acid conjugating ability of the liver in newborn and premature infants. Storey and Dutton (1955) have demonstrated that the conjugation of substances like p-aminophenol, menthol and others with glucuronic acid is catalyzed by an enzyme system in the microsomes of the liver and requires uridine diphosphate glucuronic acid (UDPGA) as the glucuronide donor. The enzymatic formation of bilirubin glucuronyl seems to involve the same system (Schmid, Hammaker and Axelrod, 1957).

A diminished glucuronide synthesis in young animals as compared with adult animals was demonstrated *in vitro* with liver tissue from mice (Karunairatnam, Kerr and Levvy, 1949), rabbits (Hartiala and Pulkkinen, 1955) and rats (Vest, 1958). The purpose of this paper is to report the results of an investigation into the capacity of the liver of full term and premature infants to form glucuronides.

Method

We chose the substance acetanilide (Antifebrin) to assess glucuronide formation. After oral administration this compound is excreted to 80% as N-acetyl-p-aminophenol-glucuronide, very little (about 4%) appears as free N-acetyl-p-aminophenol, and an insignificant part is de-acetylized in the body to aniline (Brodie and Axelrod, 1948a). This can give rise to the formation of methaemoglobin if an overdose is given. In the adult some 80% of the given amount of acetanilide is excreted in the urine within 24 hours. The dosage administered was 10 mg./kg. body weight, an amount which does not produce any toxic effects. The acetanilide was given in milk or by stomach tube. The urine was collected for a period of 48 hours, but separately for each 24-hour period. Before and several hours after the administration of the acetanilide the methaemoglobin level in the blood was examined by the method of Evelyn and Malloy (1938). P-aminophenol (free and total conjugated) was determined by the method of Brodie and Axelrod (1948b). It was found necessary, however, to repeat the extraction with ether-isoamyl-alcohol as we were unable to recover all the p-aminophenol from urine in one step. Moreover, normal colour development with phenol and sodium hypobromite occurs only if the solution is distinctly alkaline. Therefore a surplus of sodium carbonate has to be added to the bromine water.

The method of Jendrassik and Gróf (1938) was used in the micro modification of With (1943) for the determination of bilirubin in the serum. The subjects investigated were 94 premature, full term infants and older children at the Children's Hospital, Basel.

Results

Fig. 1 shows the amount of p-aminophenol in the 24-hour urine expressed as a percentage of a given dose of acetanilide in relation to the age of the children. The graph includes the regression line for full term and premature infants. It can be seen

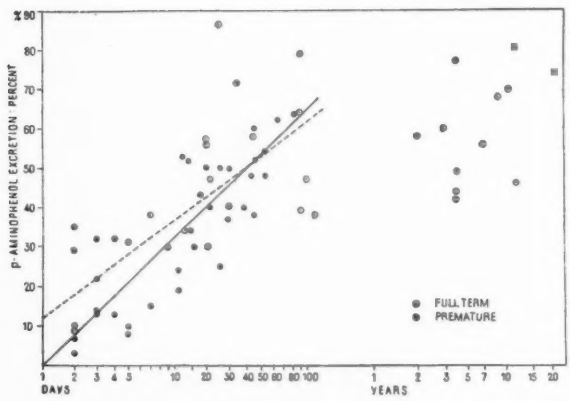


FIG. 1.—Excretion of p-aminophenol as glucuronide in 24 hours expressed as percentage of a given dose of acetanilide in relation to the age of the children.

that the excretion is much lower in newborn infants than in infancy and childhood and that premature infants have a still lower capacity to excrete a given amount of acetanilide. At the age of about 3 months the average excretion is not much below that of older children or of young adults and the difference between full term and premature infants can no longer be demonstrated. Free p-aminophenol was traceable in the urine of only a few cases and was generally well below 5% of the ingested acetanilide. Fig. 2 demonstrates how the ability to excrete acetanilide as glucuronide develops in the various premature and full term infants in the first 3 months of life. In almost every case this ability is very low in the beginning, but rises conspicuously within 10 to 20 days after birth. This ability immediately after birth is satisfactory only in a few infants (Cases 1 and 13). Figs. 3 and 4 are examples of the relationship which exists between the capacity of the newborn to eliminate Antifebrin as p-aminophenol-glucuronide and the height of the serum bilirubin concentration. An inverse relationship can be clearly demonstrated: with the increasing ability to form and excrete p-aminophenol-glucuronide the bilirubin level decreases to normal. Because of a rising bilirubin concentration in one infant an exchange transfusion was performed (Fig. 4) in order to remove bilirubin from the circulation, but with only temporary success. However, with increasing ability to conjugate glucuronic acid the bilirubin level falls steeply. One fact remains to be mentioned: Figs. 3 and 4 show two examples of the

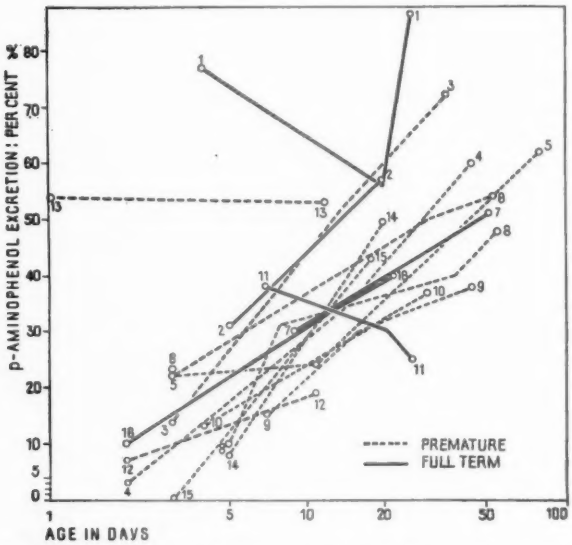


FIG. 2.—Increasing capacity of p-aminophenol-glucuronide excretion in individual premature and full term infants during the first 3 months of life.

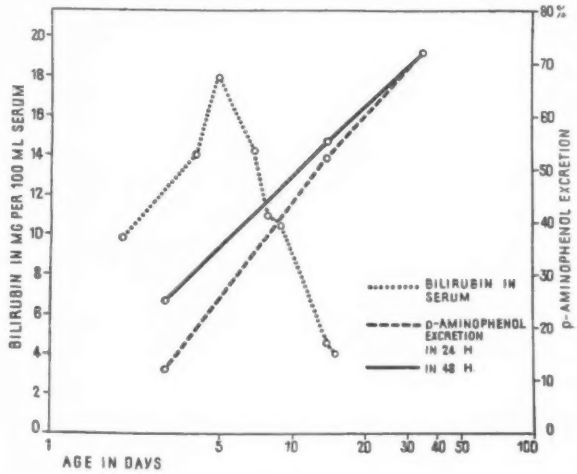


FIG. 3.

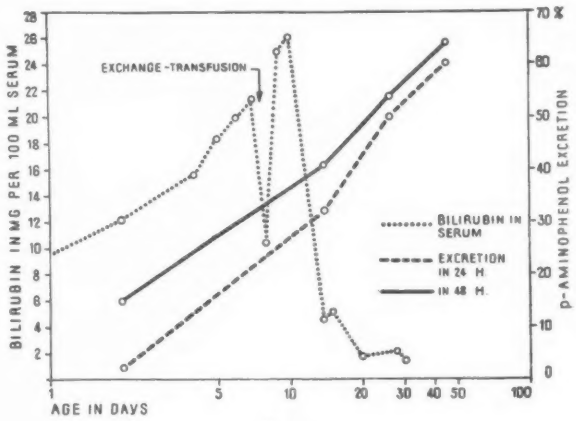


FIG. 4.

FIGS. 3 and 4.—Premature infants. Examples of the relationship between the capacity to excrete acetanilide as p-aminophenol-glucuronide and the height of the serum bilirubin concentration.

amount of p-aminophenol excreted in 24 hours as well as the cumulative excretion in 48 hours. It is noteworthy that in infants tested in the first days after birth the excretion in the first 24 hours amounts to half or less of the 48-hour value. On the other hand, in infants aged over 15 to 30 days the difference between the 24-hour excretion and the cumulative excretion in 48 hours is small. Therefore in the first few days of life the excretion is not only diminished but also much delayed. Later in infancy and childhood, no p-aminophenol can generally be demonstrated in the second urine portion because all has already been eliminated in the first 24 or even 12 hours.

Discussion

The results shown demonstrate that the ability to excrete a given amount of acetanilide is greatly diminished in the newborn and premature infant and that the normal function develops within 3 months after birth. In the first few days after birth the excretion is also very much delayed.

There are two possibilities with regard to the underlying cause of this diminished excretion in the newborn. First, the excretory capacity of the kidneys might be insufficient or secondly, the liver might not be able to conjugate glucuronic acid. A simple calculation will demonstrate that the kidney is not at fault. Assuming a low absolute p-aminohippuric acid (PAH) clearance of 20 ml./min. in a newborn baby and a PAH blood level of 2·5 mg. per 100 ml., the kidney would eliminate 0·5 mg. PAH per minute from the plasma, i.e. 30 mg. in one hour. These figures are chosen deliberately on the low side of actual measurements and in most cases the kidney is able to clear two or three times as much. Since the molecular weights of PAH and p-aminophenol-glucuronide are not very different, it is reasonable to assume that the kidney should be able to excrete at least 720 mg. of p-aminophenol-glucuronide in 24 hours. We have seen that the newborn baby is unable to excrete a dose of only 10 mg. acetanilide per 1 kg. body weight within this length of time. There can be no doubt that the excretory power of the kidney in the newborn would be adequate to meet this demand. One must conclude, therefore, that the liver of the newborn infant is unable to conjugate a sufficient amount of p-aminophenol with glucuronic acid. It must be remembered that this conjugation is necessary in order to make it possible for the kidney to excrete p-aminophenol. The same enzyme system is responsible for the conjugation of bilirubin to bilirubin glucuronide. Therefore the investigations described in this paper gave a direct indication of the cause of increased bilirubin accumulation in the newborn and of the pathogenesis of icterus neonatorum. Generally the bilirubin concentration in premature infants is high after birth. Concurrently these infants have also the lowest p-aminophenol excretion. This corresponds well with the fact that premature infants have the lowest content of bile pigment in meconium (Ylppö, 1913; Vest, 1958). As we have briefly mentioned, other functions of the liver are poorly developed in the newborn as well, e.g. the ability to excrete bromsulphalein or to conjugate benzoic acid with glycin or the formation of prothrombin and proconvertin (Loeliger and Koller, 1952; van Creveld, Paullsen, Ens, van der Meij, Versteegh and Versteegh, 1954; Vest and Meier, 1957).

In contrast with the congenital familial non-haemolytic icterus (Crigler and Najjar, 1952) in which an isolated defect of the glucuronic acid conjugating system exists (Schmid, Axelrod, Hammaker and Rosenthal, 1957) there is a deficiency in more than one metabolic liver function in the newborn baby. One of these, the insufficiency of the glucuronic acid conjugating system, accounts for the hyperbilirubinemia and gives rise to icterus of the newborn.

Summary

The capacity of the liver to form glucuronides was tested in full term and premature infants by administration of acetanilide in a dosage of 10 mg./kg. body weight and by measurement of the amount of p-aminophenol-glucuronide in the urine. Adults and older children are able to excrete about 80% of this value in 24 hours or less, whereas newborn and especially premature infants only eliminate a few % in 24 hours. Even in 48 hours the total excretion in newborn infants amounts to only about 10% or less. Within the first weeks of life the power to conjugate glucuronic acid steadily increases and by the age of 3 months normal function is generally reached.

There exists an inverse relationship between the ability to form glucuronides and the height of the bilirubin concentration in the serum. As the capacity of the liver to form glucuronides increases the serum bilirubin level begins to fall. It is concluded that this insufficiency in the formation of glucuronides by the liver might be regarded as the underlying cause of icterus neonatorum.

References

Billing, B. H., Cole, P. G. and Lathe, G. H. (1954). *Brit. med. J.* **2**, 1263.
——, ——, —— (1957). *Biochem. J.*, **65**, 774.
Brodie, B. B. and Axelrod, J. (1948a). *J. Pharmacol.*, **94**, 29.
——, —— (1948b). *Ibid.*, **94**, 22.
Creveld, S. van, Paullsen, M. M. P., Ens, J. C., van der Meij, C. A. M., Versteegh, P. and Versteegh, E. T. B. (1954). *Et néo-natal.*, **3**, 53.
Crigler, J. F. and Najjar, V. A. (1952). *Pediatrics*, **10**, 169.
Evelyn, K. A. and Malloy, H. T. (1938). *J. biol. Chem.*, **126**, 655.
Fashena, G. J. (1948). *Amer. J. Dis. Child.*, **76**, 196.

Hartiala, K. J. V. and Pulkkinen, M. (1955). *Ann. Med. exp. Biol. Fenn.*, **33**, 246.
Jendrassik, L. and Gróf, P. (1938). *Biochem. Z.*, **297**, 81.
Karunairatnam, M. C., Kerr, L. M. H. and Levvy, G. A. (1949). *Biochem. J.*, **45**, 496.
Loeliger, A. and Koller, F. (1952). *Acta haemat.* (*Basel*), **7**, 157.
Meyer, T. C. (1956). *Arch. Dis. Childh.*, **31**, 75.
Mollison, P. L. and Cutbush, M. (1949). *Ibid.*, **24**, 7.
Napp, J. H. and Plotz, J. (1949). *Arch. Gynäk.*, **176**, 781.
Obrinsky, W., Allen, E. L. and Anderson, E. E. (1954). *Amer. J. Dis. Child.*, **87**, 305.
——, Denley, M. L. and Brauer, R. W. (1952). *Pediatrics*, **9**, 421.
Perl, E. (1957). *Schweiz. med. Wschr.*, **87**, 334.
Ross, S. G., Waugh, T. R. and Malloy, H. T. (1937). *J. Pediat.*, **11**, 397.
Schmid, R. (1956). *Science*, **124**, 76.
——, Hammaker, L. and Axelrod, J. (1957). *Arch. Biochem.*, **70**, 285.
——, Axelrod, J., Hammaker, L. and Rosenthal, I. M. (1957). *J. clin. Invest.*, **36**, 927.
Storey, I. D. E. and Dutton, G. J. (1955). *Biochem. J.*, **59**, 279.
Vest, M. (1958). *Physiologie und Pathologie des Neugeborenenicterus*. In press. S. Karger. Basel and New York.
—— and Meier, W. (1957). *Ann. paediat.* (*Basel*), **189**, 282.
With, T. K. (1943). *Hoppe-Seyl. Z. physiol. Chem.*, **278**, 120.
Ylppö, A. (1913). *Z. Kinderheilk.*, **9**, 208.
Yudkin, S. and Gellis, S. S. (1949). *Arch. Dis. Childh.*, **24**, 12.

THE FIRST ARCH SYNDROME

BY

J. McKENZIE

From the Department of Anatomy, University of Aberdeen

(RECEIVED FOR PUBLICATION FEBRUARY 17, 1958)

Although disfiguring abnormalities of the face have been a problem to the plastic surgeon for many years and the accompanying embarrassment and morbidity have equally exercised the ingenuity of the psychiatrist, there is yet neither satisfactory treatment nor an adequate mask to shield the sufferer. Accordingly, the search for the cause and possible means of prevention has been intensively pursued for many years.

From an examination of the clinical features, anatomy and embryology of the following anomalies of the head and neck, it is clear that all arise from abnormal development of the first visceral arch and should be regarded as comprising a 'first arch syndrome': (*a*) The Treacher Collins syndrome or mandibulofacial dysostosis; (*b*) Pierre Robin syndrome (hypoplasia of the mandible with glossoptosis); (*c*) mandibular dysostosis; (*d*) deformities of the external and middle ear; (*e*) congenital deafmutism; (*f*) cleft lip and cleft palate; (*g*) hypertelorism; (*h*) a recently described syndrome exhibiting congenital deafness and hypertelorism.

Treacher Collins Syndrome. Berry (1889) and Treacher Collins (1900) each described patients showing a small notch at the junction of the outer third and inner two thirds of each lower eyelid, associated with 'an unusual want of prominence of the malar bones'. Subsequent writers, de Lima and Montiero (1923), Isakowitz (1927), Lockhart (1929), Waardenburg (1932), Herman (1936), van Linnt and Hennebert (1936), McEnery and Brennemann (1937), Debusmann (1940) and Mann (1943), added to the syndrome agenesis of the mandible, poorly developed eyelashes in the medial part of the lower lid, abnormalities of the external and middle ear, deafness, drooping of the outer canthus giving an antimongoloid obliquity of the palpebral fissures, microphthalmos and a marked hereditary trait. Franceschetti and Klein (1949) recognized the association of those features, proposed the term mandibulofacial dysostosis and attributed the condition to 'an inhibitory process occurring towards the seventh week of embryonic life and affecting the facial bones deriving from the first visceral arch. . . . The syndrome is of genic origin and is transmitted in an irregular mode . . . dealing with an unstable gene of occasional pleotropic, polyphaenic effect'. Hövels (1953*a*) also reviewed the subject and (1953*b*) claimed that these first arch anomalies resulted from maldevelopment of the head neural crest.

Pierre Robin Syndrome. In the newborn, hypoplasia of the mandible associated with a tendency for the tongue to block the pharynx (glossoptosis) has attracted attention because of the attendant feeding difficulties, choking fits and emaciation. Apart from their occurrence in the Treacher Collins syndrome, these features may be present alone, comprising the Pierre Robin syndrome. As described by Lenstrup (1925), Ely and Farber (1930), Davis and Dunn (1933), Robin (1934) and Lapage (1937), the condition shows a remarkable tendency to spontaneous improvement; this, and the fact that the symphysis menti is nearly vertical and the angle of the mandible nearly a right angle (Walker, 1956), have diverted attention from the purely teratogenic theory of origin to that expressed by Llewellyn and Biggs (1943), viz., that the micrognathia is purely a mechanical effect produced by the pressure of the chin against the sternum in the vertex position of the foetus; these authors went even further: they claimed that the frequent complication of cleft palate may be the result of the tongue being pushed back into the mouth and preventing the fusion of the palatal processes.

Mandibular Dysostosis. Obviously, micrognathia may occur in varying degrees, some so slight as to be unnoticed, and it is probably only in cases with a

disproportionately large tongue interfering with respiration and feeding that the condition calls for attention. Nager and Reynier (1948) did not mention glossoptosis when they described mandibular hypoplasia in association with defects of the ear; they called this syndrome mandibular dysostosis.

Deformities of the External and Middle Ear. These require no description here. Wilson (1955) in his classification observes that the more severe the defect of the auricle the more likely the involvement of the meatus, that accessory auricles and pre-auricular fistulae tend to be hereditary and that in anomalies involving the external and middle ear the most frequently involved ossicles are the malleus and the incus. .

Congenital Deafmutism. Dealing with abnormalities of the inner ear, Wilson (1955) states that they are 'inextricably mixed up with deafmutism', while Altmann (1950) describes the pathological changes found in the cochlea of two deaf mutes; there appears to be great difficulty in differentiating pathological from congenital abnormal alterations. McKenzie (1958) has shown, from audiometric examination of five cases of congenital deafmutism, that the condition is caused by an abnormality of the middle ear. On this account, and because of its association with congenital anomalies of the first visceral arch, the probability is that congenital deafmutism, also, arises from the same initial developmental fault.

Cleft Lip and Cleft Palate. Here the most likely cause is a failure or disturbance in the development of either the maxillary or frontonasal process, usually the maxillary, causing sufficient inhibition of growth to prevent approximation of these processes at the scheduled time. In cleft lip it is worth noting how the ala or alae and dorsum of the nose succeed, by dint of appreciable flattening or 'spreading', in bridging the difficult gap between the nasal process and the maxilla. Accompanying congenital lesions include anomalies of the ear, deafness, microphthalmos and asymmetry of the mandible.

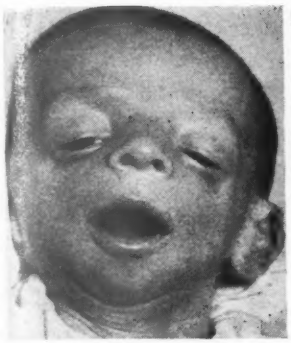
Hypertelorism. Ocular hypertelorism is a term coined by Grieg (1924) to describe the unusually wide interval between the medial canthi in two cases which he was fortunate to dissect. The following features may be seen in his illustrations: there is a wide nasal aperture, its roof formed of greatly expanded nasal bones with a small sutural bone between them; the maxillae are slender and seem stretched to their utmost to fulfil their duty of bounding the nasal aperture and, even allowing for the absence of teeth and consequent bone resorption, they are undoubtedly hypoplastic; the angle between the axes of the orbits is increased, hence the patient's difficulty when looking at near objects stereoscopically; the zygomatic bones may not be quite up to the mark developmentally but at least they have the distinction of being able to support the skull (less the mandible) when it is set on the table; in the base of the skull the unusual feature is the great width of the cribriform plates of the ethmoid and of the body of the sphenoid including the hypophyseal fossa, with persistence of the craniopharyngeal canal, the original track of Rathke's diverticulum; the greater wing of the sphenoid is narrow and no greater in size than the lesser wing, the deficiency in the temporal region resulting from this anomaly and from the rather poor development of the temporal squama being compensated for by sutural bones. Greig believed that the developmental fault lay in that portion of the cartilaginous base of the skull which gives rise to the ethmoid and the body, lesser wings and medial half of the greater wings of the sphenoid.

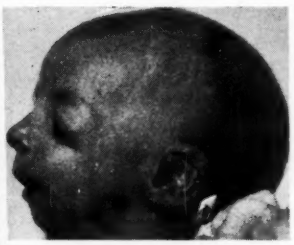
Deafmutism with Hypertelorism. Fisch and Renwick (1956) drew attention to the combination of these conditions when they appealed for help in tracing cases characterized by the following features: (*a*) lateral displacement of the inner angles of the eyes, (*b*) a broad nose root, (*c*) different colours of the right and left eyes, (*d*) white forelock and (*e*) congenital deafness.

Case Histories

The cases described below illustrate conditions comprising the first arch syndrome.

Case 1. A.R. (Figs. 1 and 2) was described and discussed by McKenzie and Craig (1955), the essential points being the receding chin with a large tongue held towards the back of the mouth, the palpebral fissures slanting downwards at the outer ends, the lower eyelid bent at the junction of the inner two thirds and outer third, eyelashes scanty in the medial two thirds, hypoplasia of the malar bones and low set ears. The child died at the age of 10 weeks from feeding difficulties and cyanotic attacks. The trunk was normal at autopsy; dissection of the head revealed absence of the zygomatic bone and the zygomatic process of the temporal bone, the maxilla completing the orbital margin and providing attachment for the masseter (Fig. 3); the squamous temporal was very small, the deficiency made up by surrounding bones and by an extra bony plaque. In the mandible the body was foreshortened, the coronoid process everted and the head elongated anteroposteriorly; the articular eminence was absent. In the ear, the incus and stapes were normal. There was no parotid gland but the facial musculature was





FIGS. 1 and 2.—Case 1.

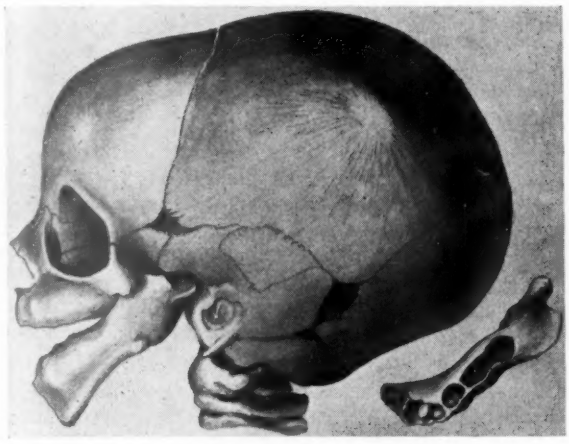


FIG. 3.—Case 1. Lateral view of skull.

well developed. The maxillary artery supplied inferior dental, posterior superior dental and middle meningeal branches but petered out before it reached the pterygo-maxillary fissure; the lower surface of the palate was supplied by the posterior superior dental artery while the nose received blood from a vessel which arose from the maxillary artery near the inferior dental artery, ran along the lower head of the lateral pterygoid muscle, entered the pterygopalatine fossa from behind and finally ran up to and through the sphenopalatine foramen into the nose. The infra-orbital artery was a branch of the ophthalmic artery.

Case 2. In G.A., aged 17 (Fig. 4), the only obvious anomaly of the head is the markedly receding mandible which reveals on the lateral radiograph (Fig. 5) an infantile appearance, namely short anteroposteriorly, an unusually wide angle, a short ascending ramus and a body lacking in depth and comprising chiefly alveolar bone; the maxilla, also, would be unusually small without its alveolar part. In the occipitomental view (Fig. 6), there is a bony deficiency in both zygomatic arches. At the age of 5 he began to complain of pain about his knees on exercise and within a year or so it was noticed that he was becoming knock-kneed. By the age of 7, radiographic examination showed anterior bowing of the femoral shafts with coarseness of the bone structure around their lower epiphyses suggesting a slight degree of rickets. Two years later there was an equally marked but opposite curvature of the upper ends of the tibiae. The lower ends of the forearm bones were also curved due to abnormal epiphyseal growth. Osteotomies in the lower limbs at the age of 15 to correct the deformities have been complicated by non-union. Renal rickets and other metabolic disorders have all been excluded. He has one sister 21 years older than himself.

Case 3. M.N., aged 9 (Figs. 7 and 8), presents marked asymmetry of the face due to absence of the ascending ramus of the mandible on the left side and absence of the left zygomatic bone with a poorly developed maxilla; the left auricle is represented by several small tubercles lying further forward than normal and the left external auditory meatus is absent. Hearing is good but probably only with the right ear. A moderate degree of hypertelorism is present, the frontonasal angle flattened, the tongue musculature poor on the left side and the palatal

FIG. 4.—Case 2.

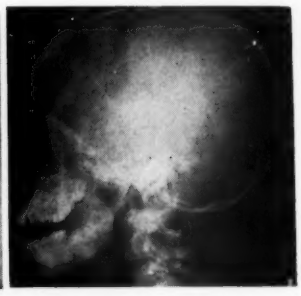


FIG. 5.—Case 2. Lateral radiograph.

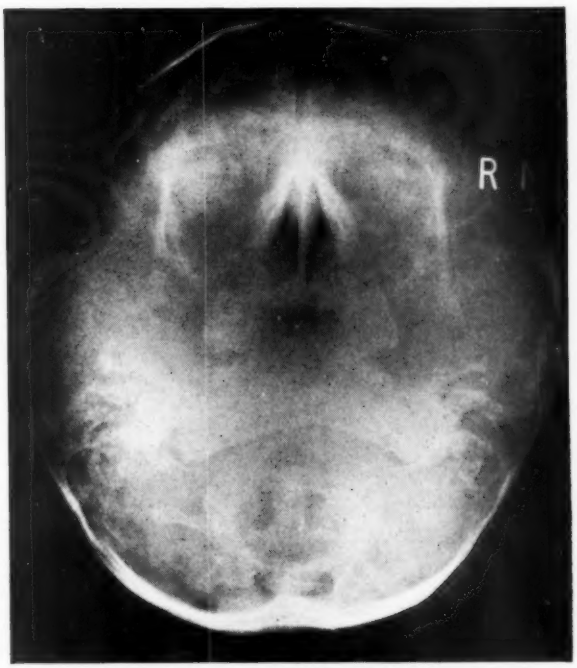


FIG. 6.—Case 2. Occipitomental radiograph.

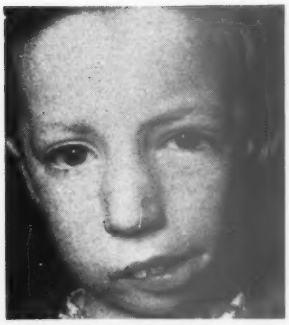


FIG. 7.—Case 3.

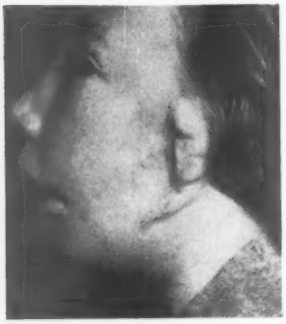


FIG. 8.—Case 3.

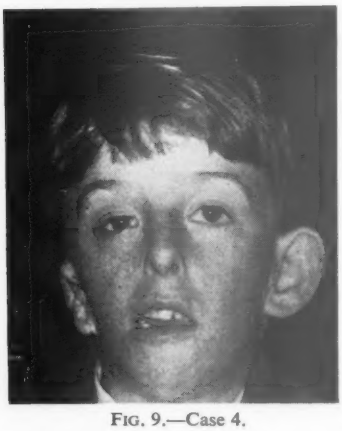


FIG. 9.—Case 4.

arch high but intact.

Case 4. A.G., aged 10 (Fig. 9), shows hemiatrophy but no bony deficiency of the jaw on the right side, irregularity of the oral mucocutaneous junction and hypoplasia of the right cheek with drooping of the outer canthus.

Case 5. A.A.M., aged 1 year, was recognized at birth as a very feeble, hypotonic, listless child with depressed bridge of nose, widely set eyes, simple low-set ears, flattened left forehead and flattening of the back of the skull on the opposite side; the soft palate was cleft and there was an obvious twist of the mandible, the tip of the chin being pushed over to the right side (Fig. 10). There has been considerable improvement since then; now it is difficult to identify the deformity of the mandible (Fig. 11) but the depressed, excessively wide bridge of the nose is still present with flattening of the bony orbital margin. Her weight as well as mental and physical development are all poor, feeding difficulties not entirely due to cleft palate restricting her progress.

FIG. 10.—Case 5.

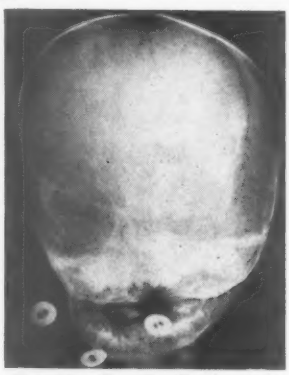


FIG. 11.—Case 5. Radiograph of skull.

Case 6. In A.M. (Fig. 12), much of the conjunctiva is exposed by the S-shaped lower lids which are atrophic and without eyelashes in their medial two thirds. The bilateral defect of the zygomatic bone is visible as well as palpable and a broadening of the interval between the medial canthi is present. The grandfather of this child, but no other member of the family, shows flattening over the zygomatic bones without eyelid defect but with deformities of the external ear and external auditory meatus.

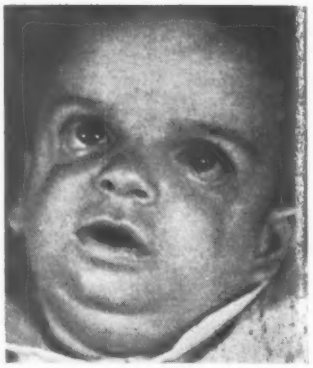


FIG. 12.—Case 6.

Case 7. R.F., aged 28, is the only member of his family showing a congenital abnormality; from birth there have been mere nodules of skin and cartilage representing the auricles; both external auditory meati are absent. Although there is considerable deafness he can carry on a reasonable conversation with the help of lip-reading and can understand what is being said on the radio. Apart from his deafness he is normal,

Case 8. B.R., aged 11, shows malformation of his right ear, deformity of the helix, antihelix and lobule with absence of the tragus and external auditory meatus. At an exploratory and reconstructive operation in 1951, it was reported that the anterior and inferior walls of the external auditory canal were missing, also the tympanic ring; the incus was the only middle-ear structure that could be identified.

Case 9. In R.A., aged 14, the left ear shows absence of the tragus and microtia, and there are two tiny accessory auricles; the right ear was markedly deformed at birth with absence of the auditory canal; hearing is diminished, more so on the right side where a conversational voice is heard at 6-8 ft. in contrast to 16-18 ft. on the left.

Case 10. E.M., aged 4 (Figs. 13 and 14), is a deafmute; the striking features in his appearance are the very wide

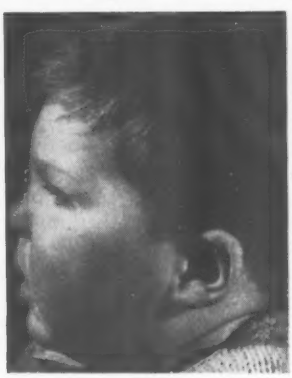


FIG. 13.—Case 10.

FIG. 14.—Case 10.

nasal bridge, the different colour of the irises, one blue and the other brown, a narrow palatal arch rising very steeply on either side but showing no cleft and a narrowness or 'pinching' of the nostrils and upper lip region. In the middle of the hair line over the forehead are a few white hairs; this white forelock, like the congenital deafness, is a marked feature in his ancestry; his mother, who declined to be photographed, is congenitally deaf and also had a white forelock when younger but her hair is now all white; she shows no hypertelorism but the frontonasal angle is nearly a straight line. The pedigree chart (Fig. 15) reveals that two brothers of the mother each have a white forelock and congenital deafness and that her father, although not deaf, had the characteristic forelock. No details are available regarding the cause of the 'wasting' in the three brothers and one sister of the mother who all died during their first year. The child's father is only partially deaf probably as a result of middle-ear disease in childhood.

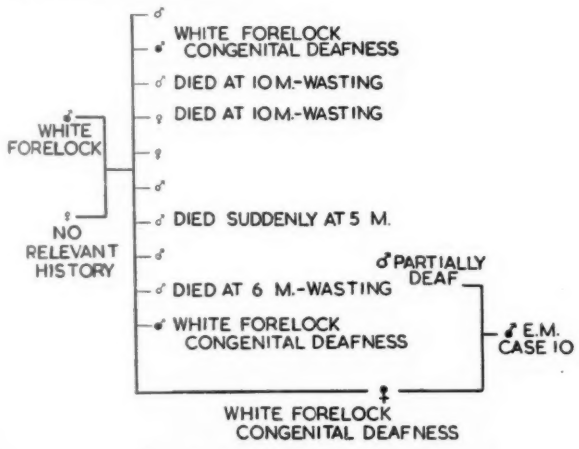


FIG. 15. Pedigree chart of case 10.

Case 11. D.S., aged 5½ (Fig. 16) is also deaf-mute and is suspected of being mentally backward. There is an anti-mongoloid obliquity of the palpebral fissures and his mother volunteers the information that he 'does not weep with his left eye'. This can be due only to hypoplasia of the lacrimal gland on that side. There is no family history of deafness or congenital abnormality.

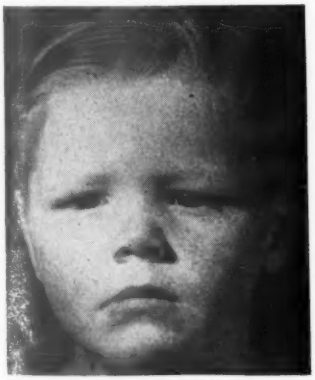


FIG. 16.—Case 11.

Embryology of the First Visceral Arch

Figure 17 shows the contributions to the face of the first (mandibular) arch and its maxillary process

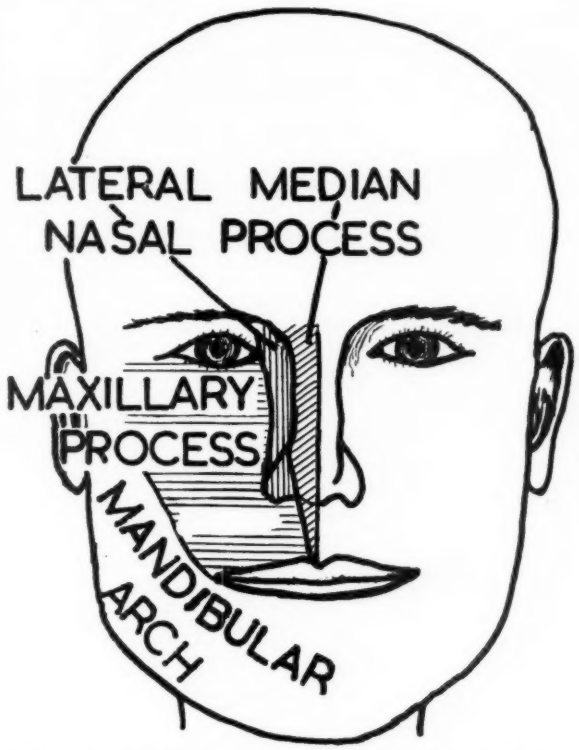


FIG. 17.—Contribution of mandibular arch to structure of face.

and of the frontonasal process. The external auditory meatus is the persistence of the posterior end of the first ectodermal groove while the middle ear and the auditory (Eustachian) tube represent the first, and possibly part of the second, endodermal pouch. Of the pinna, only the tragus and the area immediately around it derive from the first arch, the remainder from the second arch (Wood-Jones and I-Chuan, 1934). The dorsal ends of the first (Meckel's) and second (Reichert's) cartilages provide the ear ossicles, the incus and malleus from the first, the stapes from the second. Although the pterygo-quadrate cartilage (part of Meckel's cartilage seen in lower vertebrates) cannot be identified in the human embryo, two cartilaginous masses adjoining the primitive base of the skull are believed to be derivatives, namely the cartilaginous models and later the centres of ossification for the greater and lesser wings of the sphenoid bone. That for the greater wing is supplemented at a later stage by an intramembranous centre of ossification and the same is probably true for the lesser wing. Tandler (1902) and Padget (1948) have described the development of the vascular supply to the first visceral arch and its environs: after the disappearance of the first and second aortic arches, the blood supply of this region is left to small mandibular arteries arising on either side from the

dorsal aorta (the future internal carotid artery). The mandibular artery confines its activities to the maxillary process (the primitive maxillary artery); the hyoid artery supplies the second visceral arch tissues; the mandibular arch proper receives blood from the ramifications of a newly formed vessel, the ventral pharyngeal artery running forwards from the truncus arteriosus. From the hyoid artery, a newly formed vessel turns forwards through the mesodermal condensation representing the stapes and (as the stapedial artery) grows to a far greater size than its parent vessel; it then advances on the mandibular arch, thereafter dividing into two branches, one, the supra-orbital division proceeding dorsally and cranially, the other, the maxillomandibular division ventrally and medially towards the maxillary process and mandibular arch. The former division passes at first lateral to the trigeminal ganglion and then accompanies the ophthalmic artery to the orbit. The maxillomandibular vessel replaces the now dwindling primitive maxillary artery by sending one branch (the infra-orbital ramus) into the maxillary process while a second branch joins the distal end of the ventral pharyngeal artery to form the mandibular artery (the inferior dental of the adult). Ventrally, the external carotid is already growing towards the mandible and distributing on the way its more proximal branches like the lingual and the facial. Finally it joins the bifurcation of the maxillomandibular artery, takes over its two branches now called inferior dental and maxillary arteries, reverses the flow of blood in the proximal part of the maxillomandibular vessel transforming it into the proximal part of the middle meningeal artery, the distal and main part of which is derived from the supra-orbital division of the stapedial. At the point where it arises from the hyoid, the trunk of the stapedial begins to narrow becoming the superior tympanic branch of the middle meningeal artery. The original hyoid artery persists as the tiny carotico-tympanic artery. In his article Padget (1948) provided an explanation of why there should sometimes be a branch from the anterior division of the middle meningeal artery anastomosing with the ophthalmic artery or even giving origin to the lacrimal and other orbital branches; an ophthalmic branch can be traced to the eye from the supra-orbital division of the stapedial to assist in the supply of the eye and orbit; later the terminal part of the vessel is annexed by the future definitive artery and used as its lacrimal or other orbital branches.

The Etiology of the First Arch Syndrome

The detailed anatomy of Case 1 showed marked vascular anomalies and, in spite of a well-known range of 'normal' variation in such vessels, these findings are enough to incriminate the arterial system in the production of hypoplasia of the zygomatic bone, if not as the original cause then at least as an important intermediary. Only one reference can be traced in the literature to a defect of the first visceral arch region associated with a vascular anomaly: Tomes (1872) described a mandible showing marked hypoplasia of the left body and ramus with no inferior dental foramen and consequently no mental foramen on that side, 'the vascular supply of this side of the jaw was derived from several small vessels entering the front of the jaw on its inner and outer aspects'. Tomes compared his with a similar specimen described by his father 11 years before; there the canal for the inferior dental artery 'was very small and did not emerge at a mental foramen but was lost in the bone'.

From the description given above of the normal blood supply of the first arch it is clear that, in the interval (third to fifth week) between the disappearance of the first aortic arch and the full development of the external carotid artery, the first visceral arch has a hazardous existence, dependent during that time on the relay of three successive vessels, the remains of the first aortic arch, the stapedial artery with its branches and the external carotid artery and on some split-second timing on their part as one relinquishes and the next adopts the supply of that region. Before considering the numerous mishaps which may occur at this time, it is as well to recall the effect of obliteration of any large artery during adult life; provided the patient is young and healthy, arterial anastomoses with adjacent vessels can compensate for the injured artery and within a relatively short time the tissues are receiving adequate nourishment for their needs at rest but they may have to wait an appreciable period before full activity is possible. Compensatory anastomoses will be as active during embryonic life and survival will be as easily assured. These tissues, however, are not at rest; they are seething with an activity less obvious than muscular contraction but far more vital to themselves, namely growth and differentiation which are known to have a high utilization of oxygen and other nutriments.

Far too many hitches may occur in the three weeks so critical to the first visceral arch region for each to receive adequate discussion here, and only a few with their consequences will be mentioned. The stapedial artery which, after all, is a phylogenetically labile vessel and therefore likely to vary, may be very poorly developed; this implies a late start, an inadequate flow of blood and possibly an early involution and if no vessel contemporary with it or

its branches seeks to help, the maxillary process would find itself without blood after degeneration of the primitive maxillary artery; the mandible would be inhibited in its growth when the time came for the ventral pharyngeal artery to disappear; the supra-orbital ramus of the stapedial artery struggling to supply the tissues of the side of the head may be unable to assist the primitive ophthalmic vessel with the normally profuse circulation to the eye and the orbit; poor development of either branch of the maxillomandibular division may be sufficient to prevent death of the tissues in the maxillary process and the mandibular arch but barely enough to allow normal growth, while, unless the external carotid artery reaches this region before the stapedial degenerates, the same results may follow as from an inadequate supply by that artery.

All the compensatory anastomoses may develop in response to such a serious defect as a poorly developed stapedial artery and consequently no evidence of any abnormality may be apparent in later life. On the other hand a dilatory response by one of the neighbouring vessels may result in a relatively short but nevertheless crucial period of malnutrition in a region normally supplied by the stapedial. Juggle with these possibilities and it becomes perfectly clear how failure of one vessel (the stapedial) to play its full part in normal development may result in complete chaos in the subsequent development of the first visceral arch and its derivatives, or perhaps only focal derangements such as inhibition of growth in the maxilla, mandible or ear, or, if conditions at the time happen to be particularly favourable, no perceptible abnormality.

Objections to this explanation may be raised on the grounds that these abnormal events take place between the third and fifth weeks, an appreciable time before any sign of an ossification centre appears in the mandible or maxilla (sixth week) or before the appearance of the hillocks representing the pinna (also sixth week). To cause an upset in initial bone formation, however, a lapse in the maintenance of an adequate blood supply need not occur at, or immediately before, the stipulated time of appearance of the ossification centre; the latter phenomenon is merely a phase in a series of reactions which began some time previously and interference with the blood supply to the region at an earlier date may give rise to an abnormality which is only apparent later.

Genetics of the First Arch Syndrome

There are too many instances recorded of transmission through several generations for the syndrome to be explained in any other way than by hereditary factors: Debusmann (1940) found 10 members in three generations of one family, Straith and Lewis (1949) described the variations in the syndrome occurring in a mother and her four children, the father having normal features; affected brothers were reported by de Lima and Montiero (1923); a mother and daughter by Berry (1889) and a father and two daughters by Isakowitz (1927); the father of Case 1 described here has a hare lip; Case 10 reflects the features presented by his grandfather and the cases of deafmutism in one family reported by McKenzie (1958) have prototypes in their mother, father and four paternal uncles. Franceschetti and Klein (1949) concluded from their review that mandibulofacial dysostosis was hereditary.

Whether the gene responsible for the syndrome is recessive or dominant may be judged from the incidence of the syndrome; having no relationship to sex or to consanguinity, it must be regarded as dominant although there, too, modifying factors exist, such as the lapse of the syndrome in the second generation followed by its re-appearance in the third, and the many different guises it assumes in its history. These characteristics depend on the expressivity, penetrance and the specificity of the gene concerned. Expressivity is (*a*) the activity of the gene itself which depends on the quantity of some substance produced by it in initiating the reaction for which it is responsible as well as (*b*) its activity in relation to the rest of the genes and to the environment (Waddington, 1939). 'Different genes vary greatly in their response to particular environmental changes' (Gates, 1946). Penetrance is a measure of the frequency with which the characteristic features of a gene appear in the carrier while its specificity refers to the kind of effect rather than to the amount.

In this syndrome there is the unique opportunity not only of displaying the morphological sequences which lead to the anomalies in the child but also of explaining the variable expressivity and specificity and moderate penetrance of the gene. The gene, we must presume, is responsible for the maldevelopment or even suppression of the stapedial artery while the compensatory processes (anastomoses) will provide the degrees of penetrance, although other factors must be sought to explain the variability of the compensatory reactions. The results of experimental teratology can, at least partially, solve this problem. Since the time of Saint-Hilaire (1826) it has been well known that anomalies may be produced in chicks by abnormal environment such as shaking the eggs or covering them with varnish. Dareste (1891) and Féré (1899) furthered these experiments while Stockard (1909) and Spemann (1938) exploited the possibilities in the amphibian, but it was not until Hale (1935) showed that anophthalmos and cleft palate occurred

in pig embryos when the sows were fed on vitamin-A-deficient diets that the production of congenital anomalies in mammals became a common experimental procedure. Many teratogenic agents have since been used, e.g., riboflavin deficiency (Gilman, Perry and Hill, 1952; Nelson, Baird, Wright and Evans, 1956), folic acid deficiency (Thiersch, 1952; Nelson, Asling and Evans, 1952), pantothenic acid deficiency (Giroud, Lefebres, Prost and Dupuis, 1955) and ionizing radiations (Wilson and Karr, 1951; Wilson, Jordan and Brent, 1953). Ingall's (1952) remarks concerning the multiplicity of these experiments adequately sum up the present position: 'From the welter of investigations has come an ever-growing list of teratogenic agents . . . As the number rises, however, the question of specificity seems to become less important than dosage and timing of the agent used. The very diversity of teratogenic stresses and agents suggests that any substance that can kill can induce abnormal growth when acting in critical dosage at an appropriate moment of development'.

One of the most vulnerable regions for congenital abnormalities in these experimental animals is that of the first visceral arch, e.g., micrognathus, cleft lip, cleft palate, microphthalmos and anophthalmos, while the only histological investigation after deficient diets in pregnancy was carried out by Giroud, Lefebres, Prost and Dupuis (1955) on deformed limbs; they reported that 'arrest of the blood circulation in the dilated marginal veins (of the limbs) had occurred. The vascular endothelium had then disappeared and the coagulated blood had come in direct contact with the tissues'. Not only is it possible then to produce a condition like the first arch syndrome but it also appears from experimental procedures as well as anatomical findings that teratogenic effects are mediated through the vessels of the part concerned and, since the blood vessels of the first visceral arch normally provide it with a rather hazardous existence at one period, it is not surprising that this region is among the most vulnerable.

It is not suggested from such findings that the first arch syndrome is caused by dietary deficiency or conditions akin to the experimental procedures, for these were extreme and unlikely to occur naturally. It is enough to postulate a gene or genes as the initial factor inhibiting or even preventing the development of the stapedial artery, but the compensatory anastomoses of the surrounding vessels in such an emergency call for unusually large supplies of nourishment; the normal or minimal amount for normal development is unlikely to allow for compensatory reactions. The result, then, will be inhibition of growth in the area supplied by the faulty stapedial artery and its branches. The penetrance of the gene causing the first arch syndrome therefore depends on the nutritional state and diet of the mother during the first few weeks of pregnancy, even if the diet is minimal or 'adequate' the child may be abnormal because only an excellent nutritional state can successfully prevent the appearance of the anomaly. The expressivity and specificity of the gene, on the other hand, depend on the details and timing of the maladjustments occurring among the vessels concerned.

Discussion

The inherent tendency for improvement in the shape and development of the mandible seen in Case 5 and in children with the Pierre Robin syndrome requires further explanation. Throughout the normal development, which comprises not only an orderly progression of morphological changes but also a similarly regulated sequence of chemical reactions, there is a precise interval of time allotted to each item of growth or differentiation and all are closely interwoven. The growth and differentiation of an organ or tissue postponed beyond its normal period of activity will be proceeding under the stresses of an inimical environment, and the later the attempt is made the more it is likely to be suppressed entirely. Genetic influences or environmental factors, as we have seen, may inhibit any developmental process and prevent its completion or even its commencement within the specified time, and this initial setback will be perpetuated in successive stages of development in the organ or tissue in spite of attempts to make up the leeway. The growth of an organ or part of the body like the mandible may be compared with the journey of a long-distance express train after it has been delayed in the early part of its trip; the normal schedule provides it with immediate clearance at all junctions and signals but, if it be late, then it must contend with the demands of other trains which are on time and must take precedence over it. The delay is thus maintained if not aggravated, but the train will eventually reach its destination after facing the hazards of an unscheduled journey.

In Case 5 and in the Pierre Robin syndrome an early upset in the nutrition of the mandible and possibly of the other parts of the face was sufficient to retard growth but not to cause irreparable damage or prevent recovery; during the last few weeks of pregnancy the normal intra-uterine pressure was enough to distort this under-developed bone struggling under adverse conditions to make up its leeway. Only after birth (during the first year or two of life) does the mandible have the freedom to complete its development, correct the deformity and

assume its genetically determined shape. The same explanation will suffice for deformities such as club-foot, but several bones are involved in these cases and structural adaptation of unaffected tissues usually occurs before birth.

In Case 2 where an infantile mandible and defective zygomatic arches were associated with unexplained anomalies of the limb bones, there had been, during the third to fifth week of intra-uterine life, a nutritional disturbance influencing the first visceral arch, already affected by an abnormal stapedial artery, and leaving in its wake the characteristic features of the syndrome. This superimposed nutritional upset, however, also interfered with the initial capillary growth in the limb buds, inhibiting their development without altering the structural pattern. Whether there had been a distortion of the limbs caused by intra-uterine pressure and visible at birth is unknown but there is normally a distinct curvature in the legs of the newborn infant. Although during normal postnatal development, the bones are adequate to withstand the weight of the child, in this case the epiphyses and their newly formed bone were prematurely subjected to strenuous activity which was not favourable to processes striving to make up lost ground; the metaphyseal region, then, like the mandible in Case 5 before birth, yielded to the forces applied to it, forces which would not have affected normally growing bone. It should be noted also that not only are the bones of the lower limbs more distorted than those of the upper limb because of weight-bearing but also that the regions showing the curvatures are at the more actively growing ends of the bones, namely around the knee and at the wrist joint. In all likelihood, if the activities and weight of the child had been restricted up to, say the age of 8 or 10 (there are obvious difficulties and objections to such a course), these aspects of the child's development would have been in step with the growth of the limb bones and no deformity would have resulted. This is borne out by the history that the curvatures of the limbs did not increase markedly, if at all, in his teens.

Superficially, the cause of hypertelorism seems remote from the first visceral arch; closer examination, however, shows that the presenting feature, the wide interocular distance, is really a compensatory effect for poor development of the maxillary process, an effect seen also in cases of cleft lip and palate. Greig's first case showed poorly developed maxillae, unusually small squamous temporals and greater wings of sphenoid (all in first arch territory). In Case 10, the frontonasal process had spent itself in spreading or expanding laterally at the expense of its downward development and thereby provided an extremely high, slot-like palatal arch; no cleft had occurred because the palatal processes of the maxillae had succeeded in joining the nasal septum before being drawn upwards by the delayed growth of the over-taxed frontonasal process. The pinched appearance around the nostrils and upper lip arose from the same cause. A straining of the nutrition in the frontonasal process in such cases may account for the white forelock immediately above it, while variations in the blood supply to the two eyes could easily be the cause of their being different colours.

Fisch and Renwick (1956) and McKenzie (1958) showed that congenital deafmutism may occur in association with first arch deformities and the latter author demonstrated the middle ear origin of the condition. On clinical examination there is no evidence of any defect within the middle ear, hence the presumed normality of the ossicles; but the incus may be at fault because of its origin from the first arch (Meckel's) cartilage while the stapes, although a remnant of the second (Reichert's) cartilage, has the stapedial artery traversing it in the early stages of its development. The exact site of the abnormality, however, will have to await confirmation, although Wilson (1955) states that the ossicles are seldom abnormal in an otherwise normal ear but, if so, it is usually the stapes which is at fault.

Summary

Eleven cases illustrating the clinical features of eight different types of congenital anomaly or syndrome affecting the head and neck are described along with the relevant literature on each.

From a consideration of the clinical features, the anatomy described in several cases, the embryology of the first visceral arch and its environs, especially the development of the blood vessels, and, from an examination of the hereditary features, it is claimed that all the anomalies mentioned comprise one hereditary syndrome (the 'first arch syndrome') caused by a dominant gene or group of dominant genes with variable specificity and expressivity and with only a moderate degree of penetrance.

I am indebted to Professor R. D. Lockhart for his advice, help and interest during the preparation of this paper; and to the following for allowing me access to their case notes: Dr. George Swapp, Aberdeen (Case 2); Mr. A. B. Wallace, Royal Hospital for Sick Children, Edinburgh (Cases 3, 4 and 6); Dr. P. MacArthur, Royal Northern Infirmary, Inverness (Case 5); Mr. I. S. D. Thomson, Royal Aberdeen Hospital for Sick Children (Cases 8 and 9); and Dr. Dorothy Younie, Senior Assistant M.O.H., Aberdeen (Case 10).

References

Altmann, F. (1950). *Arch. Otolaryng. (Chicago)*, **51**, 852.
Berry, G. A. (1889). *Roy. Lond. ophthal. Hosp. Rep.*, **12**, 255.
Collins, E. Treacher (1900). *Trans. ophthal. Soc. U.K.*, **20**, 190.

Dareste, C. (1891). *Recherches sur la Production Artificielle des Monstruosités*, 2nd ed. Paris.
Davis, A. D. and Dunn, R. (1933). *Amer. J. Dis. Child.*, **45**, 799.
Debusmann. (1940). *Arch. Kinderheilk.*, **120**, 133.
Ely, R. C. and Farber, S. (1930). *Amer. J. Dis. Child.*, **39**, 1167.
Féré. (1899). *Cinquantenaire de la Société de Biologie*, Vol. Jubilaire, p. 360.
Fisch, L. and Renwick, T. K. (1956). *The Teacher of the Deaf*, **54**, 150.
Franceschetti, A. and Klein, D. (1949). *Acta ophthal.* (*Kbh.*), **27**, 143.
Gates, R. R. (1946). *Human Genetics*, Vol. I. New York.
Gilman, J. P. W., Perry, F. A. and Hill, D. C. (1952). *Canad. J. med. Sci.*, **30**, 383.
Giroud, A., Lefebres, J., Prost, H. and Dupuis, R. (1955). *J. Embryol. exp. Morph.*, **3**, 1.
Greig, D. M. (1924). *Edinb. med. J.*, **31**, n.s., 560.
Hale, F. (1935). *Amer. J. Ophthal.*, **18**, 1087.
Herman. (1936). *Bull. Soc. belge Ophtal.*, **73**, 60.
Hövels, O. (1953*a*). *Z. Kinderheilk.*, **73**, 532.
—— (1953*b*). *Ibid.*, **73**, 568.
Ingalls, T. H. (1952). Conference on Prematurity, Congenital Anomalies and Birth Injuries, New York Academy of Medicine, June, 1952.
Isakowitz, J. (1927). *Klin. Mbl. Augenheilk.*, **78**, 509.
Lapage, C. P. (1937). *Lancet*, **1**, 323.
Lenstrup, E. (1925). *Acta paediat.* (*Stockh.*), **5**, 154.
Lima, J. A. Pires de, and Montiero, H. B. (1923). *Arch. Anat. Antrop.* (*Lisboa*), **8**, 185.
Linnt, A. van, and Hennebert, P. (1936). *Bull. Soc. belge Ophtal.*, **73**, 57.
Llewellyn, J. S. and Biggs, A. D. (1943). *Amer. J. Dis. Child.*, **65**, 440.
Lockhart, R. D. (1929). *J. Anat.* (*Lond.*), **63**, 233.
McEnery, E. J. and Brennemann, J. (1937). *J. Pediat.*, **11**, 468.
McKenzie, J. (1958). *Brit. med. J.* In press.
—— and Craig, J. (1955). *Arch. Dis. Childh.*, **30**, 391.
Mann, I. (1943). *Brit. J. Ophthal.*, **27**, 13.
Nager, F. R. and de Reynier, J. P. (1948). *Practica otorhinolaryngo logica*, Suppl. 2, Vol. 10.
Nelson, M. M., Asling, C. W. and Evans, H. M. (1952). *J. Nutr.*, **48**, 61.
——, Baird, C. D. C., Wright, H. V. and Evans, H. M. (1956). *Ibid.*, **58**, 125.
Padget, D. H. (1948). *Contr. Embryol. Carneg. Instn.*, **32**, 205.
Robin, P. (1934). *Amer. J. Dis. Child.*, **48**, 541.
Saint-Hilaire, E. G. (1826). *Journ. Comp. du dict. de sc. Med.*, **24**, 256.
Spemann, H. (1938). *Embryonic Development and Induction*. London
Stockard, C. R. (1909). *J. exp. Zool.*, **6**, 285.
Straith, C. L. and Lewis, J. R. (1949). *Plast reconstr. Surg.*, **4**, 204.
Tandler, J. (1902). *Morph. Jb.*, **30**, 275.
Thiersch, J. B. (1952). *Amer. J. Obstet. Gynec.*, **63**, 1298.
Tomes, C. S. (1872). *Trans. odont. Soc. G.B.*, **4**, 130.
Waardenburg, P. J. (1932). *Das menschliche Auge und seine Erbanlagen*. Haag.
Waddington, C. H. (1939). *An Introduction to Modern Genetics*. London.
Walker, D. G. (1956). Unpublished M.D. Thesis. Dublin.
Wilson, T. G. (1955). *Diseases of the Ear, Nose and Throat in Children*. London.
Wilson, J. G., Jordan, H. C. and Brent, R. L. (1953). *Amer. J. Anat.*, **92**, 153.
—— and Karr, J. W. (1951). *Ibid.*, **88**, 1.
Wood-Jones, F. and I-Chuan, W. (1934). *J. Anat.* (*Lond.*), **68**, 525.

BOOK REVIEWS

Pediatric Gynecology, 4th ed. By GOODRICH C. SCHAUFFLER. (Pp. 349; 84 figures. 57s.) London: Interscience Publishers. Chicago: Year Book Publishers. 1958.

The fourth edition of this useful book has been slightly enlarged and contains many fresh illustrations. A seven-page section on female pseudohermaphroditism has been added and 'masturbation is, at last, given a monographic consideration'; no less than 17 pages! Here and there the author seems, perhaps, unduly concerned over the upbringing and *mores* of the American teenager, and his ideas on such going's-on as teenage pregnancy, masturbation, female circumcision and even clitoridectomy in that surprising country leave the (English) reviewer confused and somewhat breathless. The section, however, on the truly pathological disorders of the female child's genital and urinary systems are straightforward, clearly if wordily expressed and useful, and the appropriate aspects of endocrinology, chemo- and antibiotic therapy and treatment with steroids are all clear and up to date.

The subject is certainly worth a book to itself and this volume more than adequately fulfils its purposes.

The Compleat Pediatrician. By W. C. DAVISON and JEANA DAVISON LEVINTHAL. (Pp. vi + 257. 35s.) London: Staples Press. 1958.

The fact that seven editions have been published in America is evidence of the popularity of this book in its land of origin. Further editions have been or are in process of being published in Japan, Spain and Italy. An English edition has been considered essential and *The Compleat Pediatrician* is now published for the first time in Great Britain. The reviewer is uncertain as to what exactly is implied by the use of the term 'English edition'. The spelling employed in the title shows no departure from American practice.

There is none who can but admire the immense industry devoted to bringing this book up to date without sacrifice of its unique character. It is small wonder that Professor Davison has felt the need for assistance and he is to be congratulated on enlisting the services of his daughter, herself a paediatrician, as co-author. The original format of the book has been retained. Those conversant with earlier editions will find no difficulty in recognizing amendments and additions made in the light of recent advances in modern paediatrics. Greater use is made of practical footnotes than formerly. This is to be commended as is the introduction of a few carefully selected references.

There can be no questioning the value of this book if judiciously used as a discriminating guide to the collection of clinical facts relevant to the individual case. The volume is not to be regarded as a short cut to diagnosis or treatment. On the contrary it is an aid to memory and thoroughness. As the authors themselves emphasize, training and experience are essential to reliable evaluation of clinical facts no matter how meticulously amassed. Recognition of this fact is essential if the maximum help is to be derived from this admirable publication.

The Management of Childhood Asthma. By FREDERIC SPEER. (Pp. xii + 116; 13 figures. 36s.) London: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1958.

Any doctor, except an allergist, will read this primer with mounting impatience at the lopsided view given of children with asthma. Calm will return when he realizes that the book deals with the treatment of childhood asthma and not of asthmatic children, and that the text concerns only asthma due to specific allergens in the United States. Within these boundaries here is an excellent account of history taking, skin testing, elimination diets for food allergens, orthodox drug treatment and hyposensitization methods.

Of 315 cases studied in the mould and pollen laden atmosphere of Kansas City and its environs the recorded sensitivities were to alternaria (67·6%), ragweed (42·9%), housedust (38·1%), helminthosporium (22·5%) and grass (17·8%). All the rest rate low (cat, 4·1%; dog, 2·2%). Between the lines Dr. Speer reveals himself as a shrewd and doubtless highly effective physician, with more in his management than pure allergy, but as director of a paediatric allergy clinic he has to be loyal to the unitarian view that asthma is always due to specific allergens if we are clever enough to find them. He recognizes (and treats) 'unusual psychic stress' as a contributing factor. From the only alternative conception mentioned, that of a psychogenic origin, he dissents like most physicians and most psychiatrists. How sad that asthma and allergy clinics have to nail some special colour to the mast. The truth could be that asthma is a symptom and not a disease *sui generis* and that each case has to be studied afresh and in the broadest possible terms, although a few are purely allergic and a few neurotic. Dr. Speer recognizes that there may be widespread symptoms even outside the respiratory tract, but these are 'evidence of systemic allergy'. We close the book hearing a faint echo of the Preacher: 'Allergy, allergy, all is allergy'.

Technique Chirurgicale Infantile. By BERNARD DUHAMEL in collaboration with SIMONE SEGAUX. (Pp. 354; 289 figures. Fr. fr. 2,800.) Paris: Masson. 1957.

This book makes interesting reading because it is the work of a thoughtful surgeon with an original mind. He gives reasons for his preferred methods, and the

factual statement of his experience and results in several chapters is a welcome feature in this class of book. The work covers abdominal surgery, the neck, harelip and cleft palate but excludes thoracic lesions (except oesophageal atresia and hiatus hernia), neurosurgery (except spina bifida) and orthopaedics.

Some of the methods, however, may seem overingenious to the British reader: a technique for combined herniotomy and appendicectomy would seem of very limited value. Readers will also probably desire a larger and more detailed series of results before preferring his operation for Hirschsprung's disease to the well-tried Swenson type. Bodian is mentioned in the text on several occasions though no specific reference is given. The reviewer feels sure that the opinions attributed to him, e.g., that rectosigmoidectomy should only be considered 'dans les formes graves, rebelles au traitement classique', are quite unlike Bodian's present opinions.

The book will be interesting reading for paediatric surgeons but it could not be recommended as a text for one unfamiliar with the field.

Aktuelle Problem der Kindertuberkulose. By H. WISSLER. (Pp. viii + 71; 17 figures. D/M 12.80.) Stuttgart: Georg Thieme. 1958.

In this monograph Professor Wissler, late physician-in-chief of the Children's Sanatorium pro Juventute in Davos, Switzerland, discusses current problems of tuberculosis in childhood. Fully aware of the geographical variation in importance of such problems, he nevertheless succeeds in selecting for consideration questions of universal interest. He deals in lucid and precise language with topics ranging from recent advances in bacteriology and epidemiology to the oscillations in B.C.G. policy.

However, the therapeutic aspects of primary tuberculosis, mediastinal and cervical adenitis, tuberculous meningitis, as well as bone and joint tuberculosis, have not been overlooked. The place of the steroids in the treatment of the various clinical manifestations has been critically assessed on the basis of reports available in the literature but also on personal experience.

Each chapter is followed by a short but well-selected bibliography. The x-ray reproductions are generally good and the diagrams clear with the exception of one on page 39 (reproduced from Dubois) comparing mortality from tuberculous meningitis in cases treated with streptomycin alone with those having streptomycin + I.N.H.

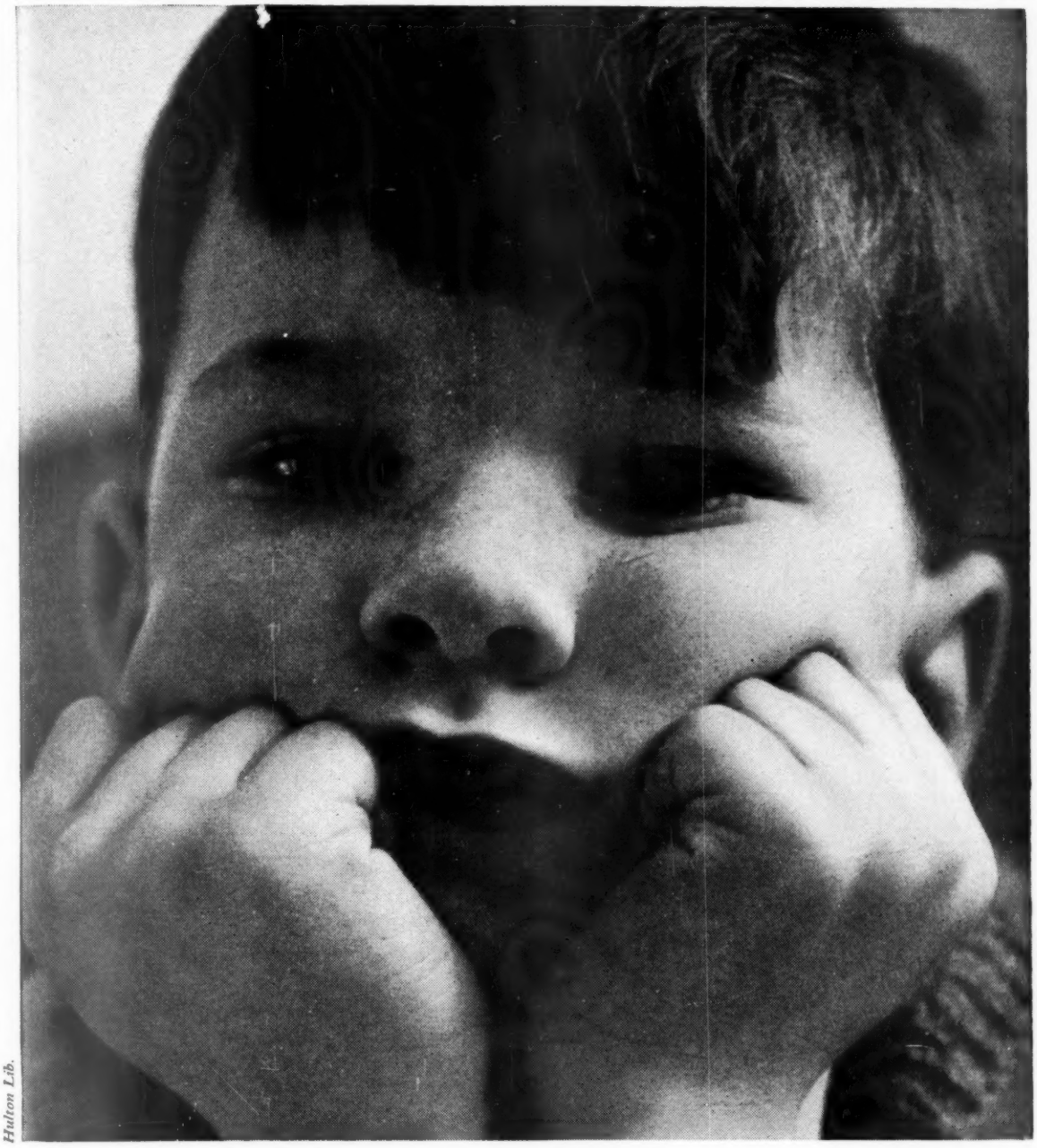
The monograph is particularly useful for those who have not had the opportunity or the time to follow the vast llterature on childhood tuberculosis but nevertheless have to treat tuberculous children in their day-to-day practice. It provides a succinctly and pleasantly written guide.

Children Under Five. By J. W. B. DOUGLAS and J. M. BLOMFIELD. (Pp. 177; 8 figures. 21s.) London: Allen and Unwin. 1958.

In 1946 a joint committee of the Population Investigation Committee and the Royal College of Obstetricians and Gynaecologists, wanting information on the maternity services and the cost of childbearing, investigated the circumstances of all confinements that took place in Great Britain during the first week in March of that year, and later published its results. At the end of the investigation there remained available a representative sample of children drawn from all types of homes in the country, and, with a certain amount of luck, the enthusiasm of a small group of workers and the financial help of various interested bodies, this sample has been and is still being followed as it grows up. Periodically during the intervening years a series of papers and monographs have appeared giving the results of various studies in this group. The latest of these, the book under review, embodies the analysis of the answer to a questionnaire sent in 1950 to the parents of a somewhat curtailed remnant of the original group of infants who were by then 4 years old. The questions related to the social class, education of parents, home arrangements and the care of children in the home, growth and illness of the infants, separation from the mother, accidents, broken homes, toilet training and some special information regarding the prematures.

The information is set out, for the most part, in tabular and statistical form, and the conclusions, 75 of them, are usefully summarized in the final chapter.

It is not easy to be sure how valuable all this information is and certainly many of the conclusions will not be news to anyone working with small children. We all agree, for instance, with conclusion no. 7 that 'a large proportion of children shared their beds particularly in Scotland and in both countries many slept either in the same bed or in the same room as their parents'; and it will come at least as useful ammunition to turn to the relevant tables and find that the figure for the 4-year-old children of England and Wales is 26% and for Scotland 51%. Again many of us suspecting that admission to hospital is usually only a minor psychological trauma, will breath a sigh of relief to read that 'a preliminary examination suggested that short periods of separation were not important, and we therefore matched (with controls) only those children who were separated for four weeks or more'. Moreover, though in the latter group there was a higher incidence of nightmares, thumb sucking, nail biting and bed wetting, there did not appear to be greater emotional instability, and this was also true of the 178 children living in homes broken by death, divorce or separation. It should be fascinating to watch the whole survey group as it grows up.



Hulton Lib.

Timothy can be a terror. Even his parents admit there are occasions when he can be difficult. They fully expected trouble over taking his medicine, for example, that last time he had tonsillitis. But they needn't have worried for, as their doctor had assured them, Tim didn't mind taking a teaspoonful of Penidural Oral Suspension every six hours for a week. Palatability is one reason why their doctor prescribes Penidural for such patients, but what he doesn't tell them is that he prescribes Penidural mainly because it is a reliable, long-lasting oral penicillin which has been clinically proven in over a million cases.

Packs :
Bottles of 60 *ml.* (300,000 *units per* 5 *ml. teaspoonful*).

Also available as tablets (200,000 *units*) *in tubes of* 20 *and bottles of* 100.

Oral PENIDURAL*

**trade mark*

Wyeth JOHN WYETH AND BROTHER LIMITED, CLIFTON HOUSE, EUSTON ROAD, LONDON, N.W.1
Pd.6

PRINTED IN GREAT BRITAIN BY HEADLEY BROTHERS LTD 109 KINGSWAY LONDON WC2 AND ASHFORD KENT